

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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The Cardiovascular and Renal Drugs Advisory Committee on March 18, 2009 voted 10 to 3 to recommend that the FDA approve dronedarone (Multaq) for the treatment of afib.

Dronedarone is a supposedly much safer analogue of amiodarone, but like amiodarone, not terribly effective. A recent trial found that it helped keep 36% of afibbers afib-free for a year. The placebo kept 25% of trial participants free of afib, so the net benefit of dronedarone was 11%. In comparison, the relatively innocuous ACE inhibitor ramipril (ALTACE) was found to keep 87% of a group of newly diagnosed lone afibbers afib-free over a 3-year period as compared to 67% "kept afib-free" by the placebo, or a 20% net benefit.

Also in this issue we get confirmation that the stroke risk among afibbers with no risk factors is very low (zero according to this study) irrespective of episode duration, and that catheter ablation is safe for elderly afibbers. Greek researchers present a very thorough review of our current knowledge about the causes of lone atrial fibrillation, and Swedish researchers confirm the deadly danger of digoxin, especially for lone afibbers.

This month also marks the release of my latest book "Lone Atrial Fibrillation: Toward A Cure – Volume VI". This 216-page book contains all the information published in the 2008 issues of "The AFIB Report" arranged in logical sections. The comprehensive subject index makes it easy to find the elusive, but important information you know is there – somewhere.

Volume VI covers subjects ranging 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 afib as well as important information about stroke risk and prevention are also covered. In addition, the results of our 2008 Ablation/Maze Survey, a comprehensive evaluation of the outcomes for 677 patients having undergone a total of 1045 procedures, and some elimination/reduction protocols found to be successful by fellow afibbers round out this book.

You can order your copy of Volume VI at <http://www.afibbers.org/volume6.htm>

Wishing you lots of NSR,

Hans

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Effectiveness of cryoballoon isolation

ROTTERDAM, THE NETHERLANDS. When the pulmonary vein isolation (PVI) procedure was first introduced it was common practice to place the lesion rings just inside the pulmonary veins. However, when it became apparent that this approach had an inherently high risk of pulmonary vein stenosis, the lesions rings were moved so as to be placed in the left atrium itself either very close to the edge of the junction between the veins and the

atrium (antrum PVI) or somewhat further out guided by CARTO or similar mapping. This approach, for all intents and purposes, eliminated stenosis, but did make it more difficult to ensure that the rings were complete and totally eliminated electrical conduction between the veins and the atrium.

In parallel with this development EP researchers were also working on an entirely different approach to avoiding stenosis, namely that of cryoablation. Pulmonary vein isolation 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 anesthesia.

A group of electrophysiologists from the Erasmus Medical Center in Holland now report on their experience using a cryoballoon catheter (*Arctic Front*, Cryocath, Quebec, Canada) and an 8-mm cryo-catheter (*Freezor Max*) also developed by Cryocath. Their clinical trial involved 141 afibbers with paroxysmal AF. Average age of the patients was 56 years, 29% were women and only 5% had structural heart disease, so this was essentially a group of lone afibbers, although 19% did have hypertension.

Pulmonary vein isolation was achieved in one procedure in 138 patients. In 33 patients a 23-mm balloon catheter was used, in 99 cases a 28-mm catheter was employed, and in 7 cases both balloons were used. In addition, the *Freezor Max* catheter was used to complete the PVI in 56 patients. The average (mean) procedure time was 3 hours and 27 minutes and mean fluoroscopy time was 50 minutes.

Eight patients (5.7%) experienced pericardial effusion (an abnormal collection of fluid inside the sac that covers the heart) and 4 patients (2.8%) experienced right phrenic nerve paralysis. All adverse events were either dealt with or resolved on their own. Patients were followed up for an average of 457 days via daily event recording, 24-hour Holter recordings and self-reporting of afib burden (number of episodes times their duration for a

specified period of time). The researchers considered the first 90 days following the procedure to be a blanking period and afib episodes occurring during this time were not included in the evaluation of ultimate success rates. Thus, the actual follow-up time was one year.

After the first procedure, 49% of the patients were afib-free without the use of antiarrhythmics. Twenty-four (17%) of the patients still on antiarrhythmics underwent a second procedure using the same equipment and protocol as used in the first procedure. The success rate for this second procedure was 54%. Thus, ultimately 58% of patients were afib-free without antiarrhythmics after an average of 1.2 procedures (20% repeat rate). The remaining 42% continued on antiarrhythmics with a much reduced afib burden. The researchers made the interesting comment that a recurrence in the first 3 months is highly predictive for recurrence after 3 months, whereas the absence of events in the first 3 months is highly indicative for a low recurrence rate. The long-term success rate was 86% in the group with no recurrence during the first 3 months versus only 41% in the group with recurrence during the blanking period.

Van Belle, Y, et al. One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace, Vol. 10, 2008, pp. 1271-76

Editor's comment: The single procedure complete success rate for this trial of cryoablation was 49%. This compares well with the 50% observed for 15 top-ranked RF ablation centers in LAF Survey 15. However, the final success rate of 58% after an average of 1.2 procedures is somewhat lower than that observed for 15 top-ranked RF institutions (65%) and significantly lower than that observed for the two top-ranked RF centers (72%). Here is should also be kept in mind that the patient population in the cryoablation trial consisted entirely of paroxysmal afibbers who are usually significantly easier to treat successfully than are those with persistent or permanent afib. It is of interest to note that the Rotterdam researchers found that recurrence of afib during the first 3 months following the procedure is a bad omen. In our September 2005 Ablation/Maze Survey (LAFS-9) we observed that the success rate among ablated afibbers who had no recurrent episodes during the first 3 months was 63% versus 37% for those who did have recurrences during the first 3 months.

Causes of lone atrial fibrillation

IOANNINA, GREECE. There is no unanimously accepted definition of **lone** atrial fibrillation (LAF). Most experts in the field define it as atrial fibrillation (AF) without underlying structural heart disease. Others define it as AF without heart disease, hypertension or other easily identifiable causes, while still others add the condition that AF patients cannot be classified as having LAF if they are over the age of 60 years. NOTE: In my opinion, including chronological age rather than biological age in a definition of a disease condition makes no sense at all. A recent international consensus statement on nomenclature and classification of AF concludes that LAF is AF in the absence of heart disease, while idiopathic AF is LAF in the absence of any disease that might possibly be a cause such as binge drinking, thyroid disorders, hypoglycemia, electrolyte imbalances, and pheochromocytoma.

A group of Greek researchers recently set out to summarize the current knowledge concerning the characteristics and possible causes of LAF. Following are the highlights of their well-documented findings:

- LAF is associated with a low risk of progression to permanent AF, mortality, congestive heart failure, and stroke/transient ischemic attack.
- LAF adversely affects the quality of life and exercise capacity of affected individuals.
- Epidemiological studies have found strong associations between LAF and obesity, sleep apnea, diabetes, metabolic syndrome, alcohol consumption, anger and hostility (in men), pulse pressure, and subclinical atherosclerosis.
- The underlying mechanism of LAF includes increases atrial stretch, imbalance in the autonomic nervous system, systemic inflammation, and oxidative stress.
- LAF is prevalent among relatively young males and most lone afibbers have the paroxysmal (intermittent) variety of the disorder. Episodes are often triggered by sleep, exercise, alcohol use, or eating.
- LAF is especially common among tall, lean and physically fit individuals and in this

group the relative significance of triggers may be greater than the atrial substrate. NOTE: This conclusion is based on Patrick Chambers' (PC) evaluation of the data from LAF Survey 11.

- The role of the autonomic nervous system (ANS) in the etiology of LAF is well documented. There is substantial evidence of the existence of an adrenergically (sympathetic) mediated form of LAF triggered by exercise and stress as well as a vagally (parasympathetic) mediated form triggered by rest and sleep.
- The relative hypoglycemia as well as the associated hypokalemia and hypomagnesemia observed during the night may increase the susceptibility to vagally-mediated LAF. NOTE: This conclusion is also based on PC's work.
- Lone afibbers tend to have elevated blood serum levels of B-natriuretic peptide (BNP).
- There is evidence that at least 15% of lone afibbers have a family history of AF. In other words, there is a strong genetic connection in LAF.
- There is some emerging evidence that LAF patients have significantly shorter QT intervals than their age- and gender-matched healthy counterparts and that this may be explained by alterations in the slow component of the delayed rectifier potassium channel (IKs).
- The association between inflammation and LAF is not clear. Some studies conclude that inflammation is a cause of LAF, while others conclude that LAF causes inflammation.
- There is some evidence that an unrecognized inflammation of the heart tissue or lining (myocarditis or pericarditis) may be involved in LAF.

Korantzopoulos, P, et al. 'Lone' atrial fibrillation: hunting for the underlying causes and links. International Journal of Cardiology, Vol. 131, 2009, pp. 180-85

Editor's comment: While the majority of the findings in the above report are already well known to regular readers of *The AFIB Report*, it is nice to see them confirmed in a prestigious journal like the *International Journal of Cardiology*. It is particularly gratifying to see the article written by Patrick

Chambers, a once-frequent poster on the Bulletin Board, quoted so extensively. A draft of the article was first published in the February 2006 issue and was discussed extensively in the Conference Room (session 55). Please see <http://www.afibbers.org/conference/session55.pdf>

Stroke risk vs. afib episode duration

COMO, ITALY. The risk of an ischemic stroke or transient ischemic attack (TIA) increases with age, hypertension, diabetes, congestive heart failure, and a history of a previous stroke or TIA. The National Registry of Atrial Fibrillation Scheme has developed a rating system (CHADS₂ index) which classifies the overall risk of stroke. Thus, being

over the age of 75 years, having hypertension, diabetes, or congestive heart failure each increases the risk by 1 point, while having suffered a previous stroke or TIA increases it by 2 points. The annual stroke risk for afibbers estimated by the CHAD-score developers is as follows:

<u>CHADS₂ Score</u>	<u>Annual Stroke Risk</u>
0	1.9%
1	2.8%
2	4.0%
3	5.9%

This estimation is based on data from 1733 patients. A later, much larger study (5089 patients) found the following stroke risk:

<u>CHADS₂ Score</u>	<u>Annual Stroke Risk</u>
0	0.49%
1	1.52%
2	2.50%
3	5.27%

Combining the data from the two sources produces the following stroke risk:

<u>CHADS₂ Score</u>	<u>Annual Stroke Risk</u>
0	0.9%
1	1.8%
2	2.9%
3	5.4%

There is also some evidence that the risk of stroke among atrial fibrillation patients with underlying heart disease increases with the duration of episodes. A group of Italian researchers have now combined CHAD score and episode duration into a new scheme aimed at further improving stroke risk prediction.

Their one-year study included 568 AF patients (aged between 60 and 80 years with 49% being male) who had had a pacemaker (Medtronic AT500) implanted to deal with sinus node disease (bradycardia-tachycardia syndrome). About half the patients had hypertension, a third were over the age

of 75 years, 8% had diabetes, 1.5% had congestive heart failure, and 1.4% had suffered a previous stroke or TIA. Nineteen percent were taking a daily aspirin for stroke prevention, while 25% were on warfarin. Thus, just over half the group did not receive anti-platelet therapy (aspirin) or anticoagulation (warfarin). Beta-blockers were prescribed for 10% of patients and antiarrhythmics for 46%.

Study participants who had been afib-free or experienced no more than one episode (lasting less than 5 minutes) over the one-year monitoring period were considered afib-free (group A). Patients with

one episode lasting more than 5 minutes, but less than 24 hours were stratified as group B, while those with one or more episodes lasting more than 24 hours were classified as group C. (NOTE: This group would presumably include permanent afibbers).

The overall annual incidence of stroke in the group with a CHAD score of 0 was 0%, although 1.1% did suffer a TIA. This finding confirms our long held belief that lone afibbers with no risk factors for stroke (as defined by the CHAD score) have an extremely low risk of ischemic stroke. The annual incidence of stroke in the groups with CHAD scores of 1, 2, and 3 or greater was 0.7%, 2.7%, and 18% respectively. Considering afib status, the annual stroke rate was 1.2% in the afib-free (group A), 0% in group B, but a rather high 2.6% in group C. By combining CHAD score and afib duration, the researchers uncovered two distinctly different "populations". The first consisted of afib-free individuals (group A) with a CHAD score of 2 or less, group B members with a CHAD score of 1 or less, and group C with a CHAD score of 0. In this group the average annual stroke risk was 0.8% - actually somewhat lower than what is considered normal for an age-matched population. Study

participants not meeting the above criteria had an average annual stroke risk of 5%.

As a separate part of the study, the Italian group simulated the results of 24-hour, 7-day, and 30-day Holter monitoring and found that this type of monitoring, in general, only picks up about 50% of the afib events actually occurring. The researchers conclude that using both CHAD score and afib duration to determine the need for anti-coagulation would result in a much better management of stroke prevention. NOTE: Two of the authors of this study are employees of Medtronic, but I see no reason to believe that this would, in any way, have influenced the outcome or reporting of the study.

Botto, GL, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. Journal of Cardiovascular Electrophysiology, Vol. 20, March 2009, pp. 241-48

Editor's comments: This study very clearly confirms that afibbers with no risk factors for stroke have a very low risk of ischemic stroke, irrespective of the duration of their episodes. As a matter of fact, this particular study found an annual stroke risk of 0% among participants with a CHAD score of 0. Even those with a CHAD score of 1, only had an average annual stroke risk of 0.7%.

Catheter ablation safe and effective for older afibbers

PHILADELPHIA, PENNSYLVANIA. As the proportion of elderly people grows in the US population so does the incidence and prevalence of atrial fibrillation (AF). Is catheter ablation (PVI) safe and effective in the geriatric population? This is the question that Dr. Marchlinski and colleagues at the University of Pennsylvania recently set out to answer.

Their study involved 1165 afibbers who underwent a total of 1506 ablations for AF (repeat rate of 29%) during the period 2000 to 2007. The patients were followed for an average of 2 years (minimum 1 year) to establish the safety and efficacy of the procedure in 3 different age groups – group A: less than 65 years old (mean age of 52), group B: aged between 65 and 74 years (mean age of 68), and group C: age 75 years or older (mean age of 77). The number of patients in each group was group A – 948 patients, group B – 185 patients, and group C – 32 patients. There were no statistically significant differences in clinical characteristics of the three groups except that the percentage of women in

group C (56%) was significantly higher than in group A (20%), and group B (34%). Also, the incidence of hypertension and structural heart disease was significantly higher in group C than in groups A and B (88% vs 56% and 68%).

Thus, the prevalence of lone atrial fibrillation (LAF) was very low in group C (12%), but fairly high in group A (44%). The stroke risk in the 3 groups was also significantly different with 72% of group C afibbers having a CHADS₂ score of 2 or more versus 12% in group A and 30% in group B. The prevalence of a left ventricular ejection fraction (LVEF) of less than 50% was 12% in group A, 7% in group B, and 16% in group C. There were no significant differences in left atrial diameter which averaged 4.4 cm.

All study participants underwent an ICE-guided segmental PVI procedure with additional lesions and right atrial flutter ablation as required. Repeat procedures were performed in 26% of patients in group A, 27% in group B, and 9% in group C. At

the 1-year follow-up, 66% of group A members were afib-free without the use of drugs. Corresponding complete success rates for group B and group C were 53% and 50%. An additional 14% of group A members were free of afib, but still taking anti-arrhythmic drugs (sotalol or Class 1 – flecainide or propafenone). Corresponding numbers for groups B and C were 22% and 23%.

Thus, the combined complete and partial success rates were 80% for group B, 75% for group B, and 73% for group C. In addition, 9% of groups A and B had experienced a 95% or better reduction in their number of episodes or experienced 6 or fewer episodes during the 1-year follow-up. The corresponding percentage for group C was 14%. Overall, 89% of group A, 84% of group B, and 86% of group C benefited significantly from their procedure. The rate of major complications (stroke, TIA, symptomatic pulmonary vein stenosis, tamponade, atrioesophageal fistula or phrenic nerve injury) was low and similar in the 3 age groups – group A 1.6%, group B – 1.7%, and group C –

2.9%. NOTE: Differences not statistically significant.

The Philadelphia group concludes that elderly patients do well with catheter ablation of their AF with afib control achieved at a rate comparable to younger patients and no evidence of an increase in risk of adverse events. They also make the interesting observation that 5% of group A members remained on antiarrhythmics following a successful procedure even though there was no indication that they needed to do so. Corresponding numbers for groups B and C patients were 13% and 14% respectively.

Zado, E, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. Journal of Cardiovascular Electrophysiology, Vol. 19, June 2008, pp. 621-26

Editor's comment: This study adds to the evidence that age, as such, is not a detriment to undergoing a safe and effective PVI procedure. If this applies to a group in which 88% had structural heart disease or hypertension, it should doubly apply to lone afibbers.

Approval of dronedarone imminent?

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

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

toxicity) has been observed in some trials, as have gastrointestinal problems like diarrhea, nausea and vomiting.

Two large clinical trials (EURIDIS and ADONIS) evaluated the effect of 400 mg twice a day on 1237 patients with atrial fibrillation. About half of the trial participants had hypertension, 25% had coronary heart disease, and just over 20% had a history of heart failure. The main results of the two trials (data combined) were:

- The median time to the first documented recurrence of AF was 116 days in the dronedarone group and 53 days in the placebo group.
- At the end of the trial (12 months from the start) 24.8% of the placebo group were still in normal sinus rhythm as compared to 35.9% in the dronedarone group.
- A pre-specified secondary end-point showed that 62.3% of dronedarone-treated patients were free of symptomatic AF recurrences versus 54% in the placebo group. Symptoms were defined as

palpitations, dizziness, fatigue, chest pain, and breathing difficulties.

- Patients in the dronedarone group had a slightly lower heart rate (average 103 bpm) during their first recurrence than did those in the placebo group (average 117 bpm).
- Rates of thyroid, liver and lung dysfunction observed over the 12-month trial period were not significantly increased in the dronedarone group. However, there was a substantially higher incidence of elevated serum creatinine levels in the dronedarone group (2.4% vs. 0.2%), perhaps indicating potential problems with kidney function.
- At the end of the trial 22.8% in the dronedarone and 30.9% in the placebo group had been hospitalized or had died (death accounted for 1% in the dronedarone group and 0.7% in the placebo group).

There were some early indications that dronedarone might not be suitable for patients with moderate to severe heart failure and ventricular dysfunction. The ANDROMEDA trial involving over 600 patients with advanced congestive heart failure proved these suspicions to be correct. In the 2 months that the trial lasted, 8% of the patients receiving dronedarone died versus 3.8% in the placebo group. Another trial (ATHENA) involving patients with less severe heart failure noted, however, that

those patients treated with dronedarone had a 16% reduced risk of death from any cause (over a 21-month period) than did those on placebo. Thus, dronedarone would seem to be generally safe, but not highly effective, in afib patients not suffering from advanced congestive heart failure. Dronedarone, of course, also has a marked advantage over amiodarone in that its half-life is only 1 to 2 days as compared to 30 to 55 days for amiodarone.

NOTE: The Cardiovascular and Renal Drugs Advisory Committee on March 18, 2009 voted 10 to 3 to recommend that the FDA approve this drug for the treatment of atrial fibrillation in patients without severe systolic heart failure. Interestingly, the 3 dissenting voices on the panel were the representatives of the patient and the consumer, and the toxicology expert.

Laughlin, JC and Kowey, PR. Dronedarone: a new treatment for atrial fibrillation. Journal of Cardiovascular Electrophysiology, Vol. 19, November 2008, pp. 1220-26

Editor's comment: Keeping only 36% of afibbers involved in the trials afib-free for 12 months is hardly an overwhelming success, especially when viewed in the context of the 25% "success rate" of placebo treatment. However, if dronedarone also proves safe in actual day-to-day use (as opposed to the strictly supervised use in clinical trials) then it should be a welcome replacement for amiodarone.

Atrial fibrillation "unmasked" following flutter ablation

ROCHESTER, MINNESOTA. It is well established that patients with atrial flutter (AFL) treated with drugs are at high risk for the development of atrial fibrillation (AF). It is not clear, however, whether a successful right atrial flutter ablation (cavotricuspid isthmus [CTI] ablation) decreases the risk of future AF development in AFL patients with no previous history of AF.

Researchers at the Mayo Clinic now report the results of a trial aimed at determining if a CTI ablation is more effective than medical treatment in preventing AF development in AFL patients. The study involved 87 atrial flutter patients (group 1) with no structural heart disease (lone AFL), 50 atrial flutter patients (group 2) with structural heart disease, and a control group of 59 atrial flutter

patients without structural heart disease who were treated with medication only (control group). All patients in groups 1 and 2 underwent a successful CTI ablation and were then, along with the members of the control group, followed for 5 years. During this time, 75% of the control group patients had one or more recurrences of AFL, while no patients in groups 1 and 2 had AFL recurrences. However, during follow-up, 32 group 1 members (37%) and 15 group 2 members (34%) developed AF. Most of the new AF cases were paroxysmal (85% in group 1 and 77% in group 2) and emerged within one year following the AFL ablation.

NOTE: There was no significant difference in the cumulative probability (Kaplan-Meier) of AF development between the control group and groups

1 and 2, thus indicating that undergoing a CTI ablation does not reduce the risk of later AF development. However, the CTI-ablated patients did get rid of their AFL and, as a result, 56% of them were able to discontinue their antiarrhythmic medications (mostly flecainide and propafenone). The need for cardioversion was also dramatically reduced in groups 1 and 2 from 62% of patients needing one or more cardioversions in the 2 years prior to their CTI ablation to only 4% needing it after.

The Mayo Clinic group concludes that the natural history of AF development in AFL patients is not changed even by a successful CTI ablation.

Luria, DM, et al. Effect of radiofrequency ablation of atrial flutter on the natural history of subsequent atrial arrhythmias. Journal of Cardiovascular Electrophysiology, Vol. 19, November 2008, pp. 1145-50

Editor's comment: A right atrial flutter ablation is usually successful and, according to this study, materially reduces the need for cardioversions and antiarrhythmic medications. Therefore, in the case of atrial flutter, there would seem to be no valid reason to prefer ongoing medical therapy to an ablation, especially since both carry the same risk of the future development of atrial fibrillation.

ACE inhibitors beneficial for afibbers with hypertension?

PALERMO, ITALY. There is growing evidence that the hormone aldosterone is involved in the genesis of atrial fibrillation (AF). Research has shown that an excess of aldosterone (aldosteronism, hyperaldosteronism) can cause potassium wasting, particularly in magnesium-deficient patients, and is a key player in structural remodeling (fibrosis) of the atria. Aldosterone is the "end product" of the renin-angiotensin-aldosterone system (RAAS), the body's main system for dealing with a fall in blood pressure that is too great to be dealt with by the autonomic nervous system alone. The formation of aldosterone can be inhibited by angiotensin converting enzyme II receptor blockers (ARBs) and its effect can be blocked by aldosterone antagonists such as spironolactone and triamterene.

Recent studies have shown that the ACE inhibitors enalapril and trandolapril reduce the risk of AF in patients with left ventricular dysfunction, while the ARBs valsartan and candesartan have been found helpful in preventing AF in patients with chronic heart failure. The ARB irbesartan combined with amiodarone increases time to recurrence after cardioversion in patients with persistent AF. Also, 'left atrial stunning', lasting a few weeks after the cardioversion of AF and probably responsible for the increased embolic events after cardioversion, is significantly reduced by pretreatment with irbesartan.

A study involving hypertensive patients with left ventricle hypertrophy showed that the risk of both new-onset AF and stroke was markedly reduced by the treatment with the ARB, Losartan. However, there is no evidence that ACE inhibitors or ARBs have any effect in preventing AF relapses in patients with normal hearts and no hypertension (lone afibbers). A significant proportion of afibbers with no underlying heart disease suffer from hypertension. Hypertension is usually treated with diuretics, alpha- or beta-blockers, calcium channel blockers, ACE inhibitors or ARBs. The authors of the report conclude that ACE inhibitors and ARBs should be considered the drugs of choice in patients with AF and coexisting clinical conditions such as hypertension, coronary disease, heart failure and diabetes mellitus.

Novo, G, et al. The role of the renin-angiotensin system in atrial fibrillation and the therapeutic effects of ACE-Is and ARBs. British Journal of Clinical Pharmacology, Vol. 66, No. 3, 2008, pp. 345-51

Editor's comment: Although there is no evidence that ACE inhibitors and ARBs are helpful in preventing new-onset afib, or in reducing episode frequency or duration in lone afibbers without hypertension, there is some indication that they may be of benefit to afibbers with hypertension and no underlying heart disease. Thus, hypertensive afibbers who are currently on diuretics, alpha-blockers, beta-blockers, or calcium channel blockers may wish to try an ACE inhibitor or an ARB instead to see if their afib burden might be reduced.

Dangers of digoxin confirmed

UPPSALA, SWEDEN. A subgroup analysis of data from the large AFFIRM trial (rate control vs. rhythm control) found that digoxin use was associated with a 42% increase in mortality. At the time, this finding was dismissed as likely being due to the drug being prescribed for patients at greater risk of death such as those with congestive heart failure (CHF). A group of researchers from Uppsala University now demolishes this myth and, as an aside, points out that, although digoxin has been routinely prescribed for atrial fibrillation (AF) patients for close to 100 years, its long-term safety has never been evaluated in this patient population.

The Uppsala study involved 60,764 patients admitted to 73 coronary care units in Sweden during the period 1995 to 2003. Of these, 21,459 were admitted with AF, 22,345 with CHF, and 16,960 with both AF and CHF. About 27% of the patients were discharged with a prescription for digoxin. Among those with only AF (no CHF) 23% were discharged on digoxin. The Swedish investigators monitored the death rate among the various patient groups and found that there was no difference in mortality (27.3%/year) in the AF and CHF group whether or not the patients were on digoxin. In the CHF group, overall mortality was 23.9%/year, but those on digoxin had an 11% higher mortality than those not on digoxin. Finally, in the AF group where overall mortality rate was 9.8%/year, the annual death rate was 42% higher among digoxin users than among those who had not been prescribed digoxin.

All mortality rates were adjusted for about 60 possible confounding variables (other possible risk factors for death). Of particular interest to lone afibbers is the finding that the detrimental effects of digoxin were far worse for relatively healthy patients

than for those with multiple risk factors. Thus, AF patients with AF and the least number of other risk factors were more than twice as likely to die within a year after leaving hospital if they had been prescribed digoxin.

The researchers conclude that digoxin is an independent risk factor for death among AF patients placed on long-term therapy with the drug. They also point out that there is no evidence that digoxin is helpful in speeding up conversion to normal sinus rhythm, or in preventing recurrence of AF episodes. *Hallberg, P, et al. Digoxin and mortality in atrial fibrillation: a prospective cohort study. European Journal of Clinical Pharmacology, Vol. 63, 2007, pp. 959-71*

Editor's comment: In my first book I described digoxin as truly "the medicine from hell" and recommended that it never be used by lone afibbers. My conclusion was based on research that showed digoxin actually promoted the occurrence of afib episodes, prolonged their duration, and hastened the progression of paroxysmal AF to permanent. As if this was not enough, digoxin has also been found to cause visual problems and to aggravate asthma. Because the "therapeutic window" for digoxin is very narrow, toxic reactions are common and it is estimated that about 6% of all users end up in hospital with a severe case of digoxin intoxication. This latest finding that digoxin use doubles the death rate among relatively healthy afibbers will, hopefully, convince readers of "The AFIB Report" to never accept a prescription for digoxin. As a matter of fact, if your GP or cardiologist recommends its use, it is high time to find another doctor.

Flutter ablation and PVI – Not enough?

MAASTRICHT, THE NETHERLANDS. Right atrial flutter (AFL) and atrial fibrillation (AF) often coexist. Some cardiologists and electrophysiologists believe that it is possible to eliminate the AF component by performing a cavotricuspid isthmus ablation (right atrial flutter ablation) only and thus avoiding going into the left atrium. Our ablation/maze surveys have consistently shown that this approach is unlikely to be successful and that 90 to 95% of afibbers still experience episodes even after a successful flutter ablation.

A team of Dutch EPs now report that even doing a standard PVI in combination with the flutter ablation is unlikely to eliminate the AF. Their clinical trial involved 36 patients with AF and at least one documented episode of sustained common-type AFL (group 1) and 62 patients with just paroxysmal AF (group 2). The average age of the patients was 50 years, 78% were lone afibbers, and 24% were women. Group 1 underwent a standard flutter ablation followed by a 6-week monitoring period and a subsequent PVI (without any additional lesions).

Group 2 patients underwent a standard PVI with no additional lesions. All procedures were performed using a cryoablation catheter (CryoCor Inc, San Diego, CA) and a duodecapolar LASSO catheter for mapping (segmental PVI).

The number of afib episodes among group 1 members was not reduced during the 6 weeks following the flutter ablation indicating, as expected, that a flutter ablation, on its own, is likely to be unsuccessful in eliminating coexistent AF. Group 1 members then underwent a PVI (cryoablation) without additional lesions. After a 3-month blanking period, the patients were followed for a further 2 years (on average). During this period, 67% experienced recurrent AF and 14% experienced recurrent atrial flutter, which was successfully eliminated with a second flutter ablation. Among the 24 patients who had recurrences of AF, 6 underwent a successful second PVI and 17 improved through the use of antiarrhythmic medications. Thus, the complete success rate in this group was 25%. In the group that underwent a second flutter ablation, 3 eventually became free of any arrhythmia, so taking group 1 as a whole the complete success rate was 31%.

During the 2-year follow-up after the 3 months blanking period, 7 patients (11%) in group 2 experienced recurrent AF, while 5 patients (8%) experienced new onset atrial flutter. The 7 patients experiencing AF breakthroughs underwent a repeat PVI after which 5 were afib-free with no drugs, and 2 were improved but still on antiarrhythmics. The 5 patients with atrial flutter underwent a right atrial flutter cryoablation after which 2 became asymptomatic, and 1 improved on antiarrhythmics. Thus, the final complete success rate in group 2 was 89%, the partial success rate (improved, but still on antiarrhythmics) 5%, and the failure rate 6%.

The authors conclude that right atrial flutter ablations, on their own, are insufficient to eliminate paroxysmal AF in patients who suffer from coexistent AF and flutter. Even adding a standard PVI (with no additional lesions) only brings the success rate to 31%. In contrast, a PVI with no additional lesions (repeated as necessary) has a complete success rate of 89% in patients with paroxysmal AF only. This could indicate that in patients with both atrial flutter and AF non-pulmonary vein triggers are the culprit behind AF or that sufficient electrical remodeling has already occurred in both atria, and thus a strategy that includes substrate modification may be required.

The authors also suggest that it is not necessary to do a routine flutter ablation as part of the PVI procedure in patients who only have paroxysmal AF since the post-procedure development of atrial flutter in this group is only 8%.

Moreira, W, et al. Can common-type atrial flutter be a sign of an arrhythmogenic substrate in paroxysmal atrial fibrillation? Circulation, Vol. 116, December 11, 2007, pp. 2786-92

Waldo, AL. Atrial fibrillation – atrial flutter interactions. Circulation, Vol. 116, December 11, 2007, pp. 2774-75

Editor's comment: This clinical trial confirms our survey findings that a right atrial flutter ablation, on its own, is unlikely to cure AF in patients suffering from coexistent AF and flutter. It also reveals that, even if the flutter ablation is combined with a PVI, without looking for triggers outside the pulmonary veins, it is unlikely to cure AF in patients suffering from coexistent AF and flutter. Thus, afibbers with coexisting AF and flutter should make extra sure that they go to the very best EP for their procedure since it will involve more than just a simple isolation of the pulmonary veins.

Ramipril for newly diagnosed lone AF

MILAN, ITALY. There is growing evidence that angiotensin II converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are effective in preventing relapses in atrial fibrillation patients with hypertension, and some forms of heart disease. However, to-date there is no evidence that ACE inhibitors and ARBs may be effective on their own in preventing afib episodes in lone afibbers without hypertension. A group of Italian researchers now report that the ACE inhibitor ramipril (ALTACE) may indeed help prevent

“newbie” lone afibbers from experiencing recurrences after their first episode.

The clinical trial involved 62 patients with a first-documented episode of atrial fibrillation (AF). All patients were successfully converted with intravenous propafenone and were then assigned to receive either a placebo or 5 mg/day of ramipril. The patients involved in the study had an extremely thorough medical examination and were declared to be true lone afibbers with no underlying diseases of

any kind and no hypertension. The average blood pressure in the placebo group at baseline was 133/75 and in the ramipril group 136/78. Left ventricular ejection fraction (LVEF) was 66% in the ramipril group and 65% in the placebo group at baseline. Left atrial diameter (left atrial inferosuperior diameter) at baseline was 4.1 cm in the ramipril group and 4.3 cm in the placebo group. Overall, it was a very healthy group of patients.

All study participants were re-evaluated every 3 months for the first year and every 6 months thereafter until conclusion of the 3-year study. During this period, 3 patients in the ramipril group and 10 in the placebo group experienced a documented afib recurrence. Furthermore, 8 patients in the control group complained of sporadic palpitations. At the end of the trial the serum potassium level in the ramipril group had increased from 4.1 mEq/L to 4.5 mEq/L, while in the placebo group it had increased from 4.2 to 4.3 mEq/L. Blood pressure and LVEF also improved in the ramipril group (from 137/78 to 128/70 and from 66% to 67%). In contrast, these values worsened in the placebo group (from 133/75 to 134/78 and from 65% to 63%). Ramipril was well tolerated by all patients and no one in the study had a thromboembolic event (TIA or stroke).

The researchers point out that ACE inhibition prevents the shortening of the atrial refractory period during the rapid atrial pacing that is observed when heart cells are exposed to angiotensin II. They conclude that the anti-arrhythmic effect of the interference with the renin-angiotensin system (RAAS) is also present in the setting of a normal heart in normotensive patients, that is, in lone atrial fibrillation.

Belluzzi, F, et al. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. Journal of the American College of Cardiology, Vol. 53, No. 1, 2009, pp. 24-29

Editor's comment: According to the official guidelines for the management of atrial fibrillation, drug therapy is not recommended for a first paroxysmal afib episode. Several LAF surveys have borne out the wisdom of this recommendation. However, based on the above research findings, it would certainly seem to be worth trying ramipril if episodes recur. It is interesting that ramipril increased serum potassium level from 4.1 mEq/L, which is borderline for an afibber, to a more robust 4.5 mEq/L, perhaps explaining one of the benefits of the drug.

Elimination/Reduction Protocol

Case No. 857

Male afibber – **53 years** of age with **mixed AF** of **13 years standing**; no underlying heart disease

No. of episodes in 6 months prior to starting protocol: **10**

Afib burden in 6 months prior to starting protocol: **60 hrs**

No. of episodes in most recent 6 months after starting protocol: **0**

Afib burden in most recent 6 months after starting protocol: **0 hrs**

Time on protocol: **60 months**

Still need to avoid triggers?: **Yes, but much less so**

Main components of effective protocol

Trigger avoidance: **Alcohol, caffeine**

Diet changes: **Eliminated alcohol and caffeine**

Supplementation: **None**

Drug therapy: **Proton pump inhibitor (Losec), propafenone, propranolol**

Stress management: **Control of stress at work**

Underlying disease conditions: **Heartburn**

Approaches to shorten episodes: **Beta-blocker + additional propafenone and propranolol**

Approaches to reduce ectopics: **Not applicable**

Background and details of protocol

1. My diet did not really change much but taking Losec changed my situation dramatically. I suffered from heartburn since my teenage days. Now I'm free from that by taking Losec daily, but I'm still refraining from spicy foods, caffeine and alcohol (other than some wine from time to time).
2. 100-milligram aspirin once a day (morning).
3. 3 times a day I take Profex (propafenone HCl) 150 mg, and Prolol (propranolol hydrochloride) 10 mg. I tried several other combinations which did not work for me. I also tried to reduce the daily dosage and that did not work.
4. I also control my stress at work better and moved to back office responsibilities.
5. I participate in sports, but I don't feel any limitations.

Overall the above program is working for me quite well and the only episodes I experienced were when I tried to change my daily dosage, and once when I was very sick with a high fever. I can't say that I have any major adverse effects, although I do yawn more frequently and feel a little sleepy at meetings. I don't know what would be the long-term adverse effects, if any.

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

E-mail: editor@afibbers.org World Wide Web: <http://www.afibbers.org>

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