

# THE AFIB REPORT

*Your Premier Information Resource for Lone Atrial Fibrillation!*

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*In this month's issue we highlight the exciting prospect of using stem cell therapy to eliminate atrial fibrillation. There is obviously still a long way to go, but results in the treatment of diabetes and heart disease are promising. Also in this issue, we discuss a recent study comparing efficacy and safety of pharmaceutical drugs in rhythm control versus radio frequency catheter ablation as initial (first-line) treatment for atrial fibrillation. Ablation comes out a clear winner, despite the authors' obfuscation of the data in an attempt to make the two approaches seem of equal value. And finally, we review the results of a Norwegian study aimed at determining the most effective rate control drug for treating permanent AF, we discuss the intriguing association between height and AF risk, and we report on the connection between inflammation and persistent AF. All this, and more, in this banner issue!!*

*Last but not least, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at <http://www.afibbers.org/vitamins.htm> - your continuing support is very much appreciated.*

*Wishing you good health and lots of NSR in the new year ahead,*

**Hans**

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Now a group of researchers from the University of Hawaii reports that a low dietary intake of vitamin D is associated with an increased risk of suffering an ischemic stroke. Their study included 7385 Japanese-American men who were 45 to 68 years old when enrolled in the Honolulu Heart Program between 1965 and 1968. At time of enrolment, all study participants completed a detailed food frequency questionnaire. Dietary intake of vitamin D ranged from 0 to 212 micrograms/day (0 – 8500 IU/day) with the average being 3.62 micrograms/day (145 IU/day).

## Stroke risk and vitamin D intake

HONOLULU, HAWAII. There is, by now, ample evidence that vitamin D deficiency is associated with many disease conditions including hypertension, insulin resistance, diabetes, infections, influenza, autoimmune diseases, cancers, cardiovascular disease, stroke, and heart failure. A study carried out by a group of researchers at Harvard Medical School concluded that having a low blood plasma level of 25[OH]D – the first metabolite of vitamin D – increases the risk of suffering an ischemic stroke (stroke caused by a blood clot) by between 50 and 100%.

Over the 34 years following enrolment, 960 study participants suffered a stroke, of which, 651 were ischemic (thromboembolic), 269 were hemorrhagic (caused by a burst blood vessel), and 40 were of unknown type. The incidence of stroke in the lowest quartile of dietary vitamin D intake (0 – 45 IU/day) was 0.64%/year as compared to 0.51%/year in the highest quartile (165 – 8500 IU/day). After adjusting for potential confounding variables including age, total daily food consumption, body mass index, hypertension, diabetes, smoking, physical activity, cholesterol level and alcohol intake, the researchers conclude that a low dietary vitamin D intake is associated with

a 27% increased risk of suffering an ischemic stroke. No association was found between vitamin D intake and the risk of suffering a hemorrhagic stroke. The researchers suggest that vitamin D supplementation may be beneficial for stroke prevention.

*Kojima, G, et al. Low dietary vitamin D predicts 34-year incident stroke. Stroke, Vol. 43, August 2012, pp. 2163-67*

**Editor's comment:** This study confirms the importance of vitamin D as an integral part of a stroke prevention program. The recently reported Nurses' Health Study observed a 2-fold reduction in the risk of suffering an ischemic stroke at a 25[OH]D plasma level of 95 nmol/L (38 ng/mL) as

compared to a level of 50 nmol/L (20 ng/mL). To reach a level of 95 nmol/L would, for most people, require supplementation with about 4000 IU/day. Vitamin D comes in two different forms – vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in poorly formulated multivitamins, as an additive to some foods, and is the form preferably prescribed by many physicians. Unfortunately, it is about 10 times less effective than vitamin D3 and is, by some researchers, considered toxic.[1]

[1] Armas, LAG, et al. *Vitamin D2 is much less effective than vitamin D3 in humans. Journal of Clinical Endocrinology & Metabolism, Vol. 89, No. 11, 2004, pp. 5387-91*

## How common are PACs?

BASEL, SWITZERLAND. Premature atrial complexes (PACs), also known as atrial extra systoles or atrial premature beats, are extremely common and can be found on 24-hour Holter monitoring in over 60% of normal adults. They are usually entirely benign and do not require treatment unless they are very frequent or result in uncomfortable palpitations. PACs originate from foci of "rogue" heart cells that decide to take on a beat of their own. Depending on when the PAC "fires" it may not be transmitted to the ventricles at all, but in some cases it may cause a pause in the normal heart rhythm, which may or may not be followed by a more forceful ventricular contraction.

PACs can be precipitated by stress, fatigue, fever, thyrotoxicosis, tobacco, caffeine, and certain other stimulants and drugs including cold medications and weight-loss preparations. PACs may also be a sign of underlying heart disease such as ischemia (angina pectoris), heart failure or myopericarditis. PACs can initiate atrial fibrillation (AF), atrial flutter and/or supraventricular tachycardia. Research has shown that these arrhythmias originate from the same focal points that generate PACs. PACs can be distinguished fairly easily on an electrocardiogram; they are characterized by a smaller and earlier than expected P wave. The P wave originates in the sino-atrial node and is the electrical impulse that initiates the heart beat.

It is known that a high level of PACs is associated with an increased risk of developing AF and suffering a stroke. What is not known are, what is a normal level of PACs and what are the factors associated with an increased level? A group of

researchers from Basel University now provides answers to these questions. Their study, part of the Swiss Study on Air Pollution and Lung Disease in Adults, involved 1742 participants aged 50 years or older who underwent 24-hour Holter monitoring. The main findings of the study were:

- 99% of study participants had at least one PAC over the 24-hour monitoring period.
- The number of PACs increased with age with participants between the age of 50 and 55 years experiencing an average of 0.8/hr as compared to those over the age of 70 years who experienced an average of 2.6 PACs/hr.
- Compared with individuals with a PAC frequency below 1.27/hr, individuals with a frequency at or above 1.27/hr were older, had a higher systolic blood pressure, a higher prevalence of cardiovascular disease, a higher level of BNP (brain natriuretic peptide), and a lower education level.
- Individuals with higher PAC frequency also experienced significantly more PVCs (premature ventricular complexes) and had greater heart rate variability.
- There was an intriguing correlation between height and PAC frequency with taller individuals having significantly more PACs than shorter individuals. The researchers

speculate that tallness may be associated with a larger left atrium, but also suggest that taller individuals may have elevated electric activity.

- Moderate physical activity and higher HDL cholesterol levels were both associated with less PACs. The researchers speculate that HDL levels may influence the composition of cell membranes, a major determinant of cell excitability.
- There was no correlation between PAC frequency and hypertension, or between PAC frequency and body mass index.

*Conen, D, et al. Premature atrial contractions in the general population: frequency and risk factors. Circulation, October 9, 2012 [Epub ahead of print]*

**Editor's comment:** It is interesting to note that individuals without AF generally experienced maybe one or two PACs an hour, whilst some afibbers report experiencing dozens or even hundreds of PACs and PVCs an hour. Fortunately, the incidence of PACs and PVCs can often be substantially reduced by ensuring optimum magnesium and potassium status.

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## Stem Cells 101

Stem cells are unique in that they are capable of dividing and renewing themselves for long periods. They are not specialized as to their function, but can be changed into cells with specific functions (differentiated cells) such as blood cells, brain cells, muscle cells, heart cells (cardiomyocytes), etc. It is this ability to change into cells with specific functions capable of replacing ailing or missing cells that underlies the hope they can ultimately be used to cure a vast number of diseases from diabetes to cancer and heart disease.

There are two types of stem cells.

- **Embryonic stem cells** are harvested from embryos that are surplus from in vitro fertilization procedures.
- **Adult stem cells** are undifferentiated, dormant cells found among the usual differentiated cells in tissues and organs that are able to renew themselves. The primary purpose of adult stem cells is to maintain and repair the tissue in which they are found.

Stem cells are classified as pluripotent, multipotent or induced pluripotent.

- **Pluripotent stem cells** can differentiate into any type of cell found in the body except those needed to support and develop a fetus in the womb. Embryonic stem cells are pluripotent.
- **Multipotent stem cells** can only differentiate into a limited number of different cells with specific functions. Some, but by no means all, adult stem cells are multipotent.
- **Induced pluripotent stem cells (iPSCs)** are adult stem cells that have been genetically reprogrammed to behave like an embryonic cell. At present it is not clear if iPSCs are totally equivalent to natural embryonic stem cells.

Finally, stem cells may be allogeneic or autologous.

- **Allogeneic cells** are obtained from usually young, healthy donors, often from bone marrow. These cells have the advantage of being healthy, but carry the risk of being rejected by the recipient's immune system.
- **Autologous cells** are obtained from the intended recipient and reimplanted once they have been "cleaned up" and multiplied by laboratory culture. These cells have the advantage of "being known" to the recipient's immune system but may, because they are usually older, carry genetic faults induced through DNA damage.

Bone marrow is a particularly rich source of stem cells. One type, called a hematopoietic stem cell, is able to develop into many different types of blood cells including platelets and red and white blood cells. It is possible, but still debated, that hematopoietic stem cells can also develop into other cells with heart cells being of particular interest.

Stem cell therapy or regenerative/repairative medicine is a rapidly evolving field. Basically the idea behind it is that by injecting stem cells into diseased organs or tissue the stem cells will differentiate into new, healthy cells with the specific function of the surrounding cells and thus result in repair or rejuvenation of the targeted organ or tissue. The way differentiation of stem cells work is intriguing indeed. Apparently the physical contact between the cells of the targeted organ or tissue and a stem cell sets in motion a complex chain of events that through several cell divisions transforms the stem cell into a cell with the desired specific function.

Considerable advances have been made in the treatment of diabetes via the introduction of stem cells to replace ailing or destroyed beta-cells[1,2]. Two clinical trials, SCIPIO and POSEIDON, recently reported encouraging results from the injection of stem cells into the heart muscle of heart failure patients and heart attack survivors[3,4].

There is also emerging evidence that stem cell therapy may be useful in creating biological pacemakers (replacing implanted ones), repairing malfunctioning AV nodes and eliminating cardiac arrhythmias, such as atrial fibrillation, through biological ablation[5]. British cardiologists recently reported a case where a patient with permanent atrial fibrillation returned to normal sinus rhythm after an injection of hematopoietic stem cells directly into the vein of Marshall[6].

## References

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4. Hare, JM, et al. *Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy. Journal of the American Medical Association, November 6, 2012 [Epub ahead of print]*
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6. Lyne, JC, et al. *Stem cell infusion into the vein of Marshall. Europace, Vol. 13, March 2011, p. 438*

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## **Stem cell therapy for atrial fibrillation?**

UTRECHT, THE NETHERLANDS. It is generally accepted that lone atrial fibrillation (LAF) may develop when an overly sensitive heart tissue is combined with a dysfunctional autonomic nervous system and a trigger such as stress (involving excessive secretion of cortisol and aldosterone), caffeine (involving excessive adrenergic response), etc. Trigger avoidance is often effective in reducing AF frequency and catheter ablation and maze procedures isolate or destroy heart tissue which serves as starting points and as the substrate for AF. There is growing evidence that paroxysmal (intermittent) AF is involved in the formation of fibrotic heart tissue which, in turn, hastens the

progression of paroxysmal AF to the persistent and permanent forms. At present, the only way of dealing with abnormal heart tissue enabling LAF is to destroy part of it. This may now change with the advent of stem cell therapy.

A group of Dutch researchers recently presented a review of the current state of the art concerning stem cell therapy and cardiac arrhythmias. They outline three areas of current interest:

- Biological pacemakers
- AV node repair
- Biological ablation

The goal of developing biological pacemakers is to replace current electronic pacemakers which need to be implanted, have their batteries replaced periodically, and are prone to lead failures. Animal experiments have shown that injections of stem cells into specific structures of the heart, notably the sino-atrial (SA) and atrioventricular (AV) nodes with their associated bundles of His and Purkinje fibres (see *Heart Rhythm 101* in the Research Reports section at <http://afibbers.org/resources/index.htm> for further explanation) can restore normal sinus rhythm and eliminate the need for pacemaker implantation.

The AV node is the only connection between the atrial and ventricular part of the cardiac conduction system and plays a vital role in ensuring normal sinus rhythm. Although the art of repairing dysfunctional AV nodes through stem cell injections is still very much in its infancy, preliminary experiments have shown that it is possible to precisely inject stem cells into selected parts of the node using techniques similar to those used in catheter ablation.

The aim of biological ablation is to replace current catheter ablation and surgical procedures with stem cell-based techniques aimed at suppressing the excitability of the arrhythmogenic substrate by

transplanting cells that have been engineered to contain specific ion channels, in this case, channels for the inward rectifier potassium current. Animal experiments have proven the feasibility of this approach and resulted in increasing the local effective refractory period (a measure of reduced excitability and a commensurate reduction in the risk of AF). Whilst biological ablation certainly is an exciting prospect, there is still a very long way to go before it becomes a practical approach to curing AF.

*Blank, AC, et al. Rewiring the heart: stem cell therapy to restore normal cardiac excitability and conduction. Current Stem Cell Research & Therapy, Vol. 4, No. 1, 2009, pp. 23-33*

**Editor's comment:** The field of stem cell therapy is certainly an exciting and rapidly progressing one! However, there are obviously still lots of questions to be answered and problems to be solved. As an example, the work on stem cell therapy to regenerate failing heart muscles revealed that the stem cells used also removed fibrosis and dissolved scar tissue. Thus it is conceivable that this type of stem cell therapy might interfere with the lesions created in previous catheter ablations and maze procedures.

## Stem cells stop permanent AF

LONDON, UNITED KINGDOM. The vein of Marshall (VOM) is part of the heart's venous system and drains into the coronary sinus. It is located on the back wall of the left atrium and may exhibit focal electrical activity that can initiate atrial fibrillation (AF). The focal points can be eliminated by catheter ablation or, in some cases, by ethanol infusions (vagal denervation) into the vein.

A team of cardiologists at Royal Brompton Hospital now report a case where injection of hematopoietic stem cells into the VOM eliminated long-standing persistent AF. The patient was an 84-year-old man with a 4-year history of permanent AF. He had previously undergone aortic and tricuspid valve surgery and had also had a coronary bypass operation. His left atrium was grossly enlarged with a diameter of 69 mm (6.9 cm).

Stem cells were harvested from his own bone marrow and after suitable preparation injected

directly into the VOM through the coronary sinus. Twenty days following the procedure, the patient returned to normal sinus rhythm and has remained AF-free for 15 months. The research team calls for further studies to determine whether stem cells delivered to the VOM have a role in the treatment of AF, either through transdifferentiation (conversion of hematopoietic stem cells into heart cells) or by vagal denervation (ablation of ganglionated plexi). For more on stem cells, please see *Stem Cells 101* in the Resources Section at [www.afibbers.org/resources/index.htm](http://www.afibbers.org/resources/index.htm)

*Lyne, JC, et al. Stem cell infusion into the vein of Marshall. Europace, Vol. 13, March 2011, p. 438*

**Editor's comment:** This fascinating case history adds to the accumulating evidence that stem cell therapy may, in the not too distant future, emerge as a viable alternative to drug therapy, and catheter-based and surgical procedures for the elimination of AF.

## Best rate control drugs for permanent AF

OSLO, NORWAY. Permanent (long-standing persistent) atrial fibrillation (AF) is defined as AF that cannot be terminated by electrical cardioversion, or by the use of pharmaceutical drugs. Thus it makes no sense to prescribe antiarrhythmics to permanent afibbers since the only effects they will have are adverse. This also applies to digoxin (Lanoxin). Rate control drugs, specifically beta-blockers and calcium channel blockers can, however, be useful in bringing down the heart rate and thus making the patient more comfortable.

A group of Norwegian physicians now report on a study they did to determine the most effective rate control drug. They evaluated four common rate control drugs in a group of 60 permanent afibbers (70% male) with an average age of 71 years. To be included, the participants had to have a resting heart rate in excess of 80 bpm and a minimum heart rate during the day of 100 bpm. Patients with heart failure, ischemic heart disease (angina), renal failure or liver failure were excluded. The patients were randomized to receive one of the following drugs for 3 weeks:

- Metoprolol (*Toprol*) slow-release tablets – 100 mg/day
- Diltiazem (*Cardizem*) sustained-release capsules – 360 mg/day
- Verapamil (*Isoptin SR*) modified release tablets – 240 mg/day
- Carvedilol immediate-release tablets – 25 mg/day

Following a 2-week washout period, they were assigned another one of the four drugs, and so on, until each patient had tried all four drugs. Before starting the trial and on the last day of the four treatment periods, the heart rate at rest and the average 24-hour heart rate were measured (with ECG and Holter monitoring respectively) and the patients completed questionnaires regarding arrhythmia-related symptoms. The questionnaire rated frequency (from 0 to 4) and severity (from 1 to 3) of 16 symptoms potentially associated with AF, thereby generating frequency and severity scores ranging from 0 to 64 and 0 to 48, with higher scores representing worse symptoms. Results of the trial were as follows:

	Heart Rate (average)			Symptom	
	Resting	24-hour	Night-time	Frequency	Severity
Baseline	95	96	79	13.4	8.1
Diltiazem	77	75	66	10.5	6.0
Verapamil	82	81	76	11.3	7.3
Metoprolol	81	82	72	12.0	7.4
Carvedilol	78	84	76	12.6	8.1

It is clear from this data that the sustained-release diltiazem is the optimum rate control drug for permanent afibbers. It is of interest to note that the time spent with a heart rate above 110 bpm was also reduced very significantly with diltiazem (from 266 minutes at baseline to 32 minutes with diltiazem). Also noteworthy is the finding that women tended to report a significantly greater frequency and severity of symptoms, both at baseline and after treatment. The Norwegian researchers conclude that diltiazem is the most effective drug for reducing heart rate in patients with permanent AF. It also significantly reduces arrhythmia-related symptoms whereas beta-blockers do not.

*Ulimoen, SR, et al. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. American Journal of Cardiology, October 27, 2012 [Epub ahead of print]*

**Editor's comment:** It is interesting that the Norwegian research team included the following statement in the article: "The present study was initiated by the investigators and performed without the cooperation or financial support from the drug companies." This is indeed a rare occasion these days!

## Height and atrial fibrillation

SEATTLE, WASHINGTON. In our very first LAF Survey (February 2001), it was noted that male afibbers tended to be significantly taller (183 cm or 6 ft) than the average US male (178 cm or 5 ft 10 in). Corresponding figures for female afibbers and average US females were 168 cm (5 ft 6 in) and 164 cm (5 ft 4.6 in). LAF Survey 11 (November 2005) was carried out in cooperation with Patrick Chambers, MD to follow up on this finding. The results are discussed in Dr. Chambers' report "*LAF versus AF: Shape Matters*" [www.afibbers.org/resources/LAFvsAF.pdf](http://www.afibbers.org/resources/LAFvsAF.pdf) and confirmed the significant difference in height between lone afibbers, both male and female, and the population average. Dr. Chambers' work was subsequently published in *Medical Hypotheses* (Patrick W. Chambers, Lone atrial fibrillation: Pathologic or not? *Medical Hypotheses*, Vol. 68, No. 2, 2007, pp. 281-87).

Now a group of researchers from the University of Washington confirms that taller men and women are more likely to have, or develop, atrial fibrillation (AF) than are men and women of average height. Their study included 5860 men and women enrolled in the Cardiovascular Health Study, a cohort study of older US adults followed for a median of 13.6 years (women) or 10.3 years (men), of which 66% had hypertension, and 19% had cardiovascular disease. At baseline there were 157 (2.7%) cases of AF amongst the 5860 participants. During follow-up of 5117 participants, an additional 684 women and 568 men developed AF for a total incidence of 24.5%.

After adjusting for a significant number of possible confounders, the researchers found a 26% increased risk of developing AF for each 10 cm (4 in) of height above normal. The increased risk for women for 10 cm increase was 32%. Left atrial

dimension, commonly thought to be the primary mediator of height-induced AF, was not significantly correlated with height.

The researchers speculate that the association between height and risk of AF may be genetically determined as two AF-associated genes, PITX2 and ZFX3, are also associated with growth pathways. They conclude that independent of gender increased height is significantly associated with the risk of AF.

Rosenberg, MA, et al. *The impact of height on the risk of atrial fibrillation*. *European Heart Journal*, Vol. 33, 2012, pp. 2709-17

**Editor's comment:** It is gratifying to see our work confirmed, although it would have been even better if the authors had acknowledged Dr. Chambers' earlier work. The authors made a statement that really caught my attention – "*A recent study[1] found that increased birth weight was significantly associated with the development of AF in women.*" Combining this finding with the finding in our LAF Survey 14, which showed that the only variable predicting whether or not participants had been able to find a way, other than ablation or surgery, to eliminate or materially reduce their AF burden was birth weight. A higher birth weight was associated with a complete inability to benefit from natural approaches to AF reduction/elimination. If higher birth weight is genetically associated with increased risk of developing AF, would it not make sense that high birth weight individuals would have more difficulty reducing their AF burden by natural means?

[1] Conen, D, et al. *Birth weight is a significant risk factor for incident atrial fibrillation*. *Circulation*, Vol. 122, 2010, pp. 764-70

## Persistent atrial fibrillation and inflammation

GRONINGEN, THE NETHERLANDS. Persistent atrial fibrillation (AF) is defined as AF lasting longer than 7 days, but amenable to cardioversion (chemical or electrical). Unfortunately, approximately 50% of afibbers undergoing electrical cardioversion experience recurrence within the first month following the procedure. It is believed that electrical and structural remodelling of the left atrium is at least partly responsible for the high

recurrence rate. There is also evidence that C-reactive protein is associated with an increased risk of recurrence after electrical cardioversion.

A group of researchers at Groningen University recently completed a study aimed at determining the variables affecting recurrence rate in a group of 100 afibbers with recent onset (median 4 months since diagnosis) persistent AF. All study



participants had suffered from AF for less than a year and thus presumably had experienced minimal electrical and structural remodelling. The average age of the patients was 65 years, 74% were male, 67% had hypertension, 18% had coronary artery disease, and 20% had been treated for heart failure. Immediately prior to cardioversion, 99% of participants were on warfarin, 89% were on beta-blockers, and 74% were taking an ACE inhibitor or ARB (angiotensin receptor blocker). At cardioversion patients had been in AF for an average (median) of 3 months.

Eighty-six patients underwent electrical cardioversion which was successful in 88% of cases. Four patients underwent chemical conversion, 3 had a pulmonary vein ablation, and 7 converted spontaneously during treatment with antiarrhythmic drugs. During the following year, AF recurred in 59 patients (59%) with 30 patients experiencing early recurrence (within an average of one week from cardioversion). AF became permanent, i.e. not amenable to cardioversion, in 29 patients during the first year of follow-up.

An elevated baseline level of interleukin-6 (IL-6), an important marker of inflammation, and previous or present smoking were associated with an increased incidence of early recurrence. An elevated level of transforming growth factor-Beta1 (TGF-Beta1), an

important signalling molecule involved in structural remodelling and fibrosis, and early AF recurrence predicted progression to permanent AF. Somewhat surprisingly, and unexplained, a higher left ventricular ejection fraction was also associated with a greater risk of progression to permanent AF.

The researchers point out that it is still not clear whether inflammation causes AF or AF causes inflammation, but nevertheless conclude that anti-inflammatory treatment may help prevent early recurrence of recent onset persistent AF after cardioversion.

*Smit, MD, et al. Role of inflammation in early atrial fibrillation recurrence. Europace, Vol. 14, 2012, pp. 810-17*

**Editor's comment:** Although the authors did not comment on this, there would appear to be a significant benefit associated with being on ACE inhibitors or ARBs prior to cardioversion. Only 57% of patients experiencing early recurrence were on these drugs, whilst 81% of patients not experiencing early recurrence were on them. Thus it is possible that taking these drugs as well as a natural anti-inflammatory prior to cardioversion may help prevent early recurrence. It is also very important to be replete in potassium and magnesium prior to the procedure.

## Antiarrhythmics vs ablation

AARHUS, DENMARK. The battle continues between proponents of antiarrhythmic drugs and catheter ablation as first-line treatment for paroxysmal atrial fibrillation (PAF). At present, it would appear that a trial of one antiarrhythmic drug is warranted before proceeding with ablation. It is hoped that the large CABANA trial now enrolling participants will result in a firm recommendation as to first-line treatment. In the meantime, it is worth pondering the results of the MANTRA-PAF clinical trial which involved 294 patients with PAF treated at centers in Denmark, Finland, Sweden and Germany.

The average age of the patients was 55 years, 70% were male, 7% had structural heart disease or coronary artery disease, and average left atrial diameter was 40 mm. The study participants, none of whom had undergone ablation or been treated with antiarrhythmics prior to enrolment, were randomized into two groups – the radio frequency

catheter ablation group (146 patients) and the rhythm-control group (148 patients).

Members of the ablation group underwent an average of 1.6 anatomically-guided pulmonary vein isolation procedures with an additional left atrium roof line and tricuspid isthmus (right atrial flutter) ablation as required. At the 24-month follow-up, 9% of the ablation group members were receiving antiarrhythmic drug therapy. Patients in the rhythm-control group were initially treated with 200 mg/day of flecainide or 600 mg/day of propafenone or, in case this was contraindicated, with 200 mg/day of amiodarone or 160 mg/day of sotalolol.

If the initially assigned drug therapy failed, more aggressive drug therapy (amiodarone?), cardioversion or catheter ablation was allowed. Fifty-four patients (36%) in the rhythm-control group underwent a mean of 1.6 ablation procedures with the first taking place about 9 months following



inclusion in the study. NOTE: The final study results were based on *intention-to-treat*; in other words, even though 36% of the group had undergone a mean of 1.6 ablation procedures, they were still considered to be part of the rhythm-control group when comparing the efficacy of ablation and rhythm control.

The burden of AF (percent time spent in AF) was measured via 7-day Holter monitoring at 3, 6, 12, 18 and 24 months. The AF burden was not significantly different in the two groups at 6, 12, and 18 months (13% in ablation group and 19% in rhythm-control group); however, at 24 months the ablation group fared significantly better at 9% vs 18%. At 24 months, 85% of patients in the ablation group were in normal sinus rhythm (NSR) as compared to 71% in the rhythm-control group. However, as mentioned above, these numbers are based on *intention-to-treat*. In actual fact, at the 2-year follow-up, 76% of the ablation group patients were in NSR without the use of antiarrhythmics, whilst only 35% of those in the rhythm-control group were in NSR without having undergone 1 or more ablations.

Serious adverse events possibly related to AF therapy occurred in 11% of patients in the ablation group vs 8% in the rhythm-control group. One death from stroke, probably related to the procedure was observed in the ablation group. The authors

conclude that an initial strategy of ablation as compared with rhythm control showed no significant difference in the cumulative burden of AF over a period of 2 years. NOTE: The list of potential conflicts of interest between the authors and ablation equipment and drug manufacturers is extensive.

Nielsen, JC, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. **New England Journal of Medicine**, Vol. 367, October 25, 2012, pp. 1587-95

Stevenson WG and Albert, CM. Catheter ablation for paroxysmal atrial fibrillation. **New England Journal of Medicine**, Vol. 367, October 25, 2012, pp. 1648-49 (editorial)

**Editor's comment:** This clinical trial clearly highlights the problem of reporting results on an *intention-to-treat* basis. In other words, ignoring the fact that 9% of the ablation group members were on antiarrhythmics and 36% of the rhythm-control group had undergone one or more ablations at the final follow-up. It is clear from the trial, based on a 2-year follow-up, that radio frequency catheter ablation is a better first-line treatment strategy than rhythm control. However, trying an antiarrhythmic drug before deciding on an ablation is still a viable option in view of the current, rapidly evolving ablation techniques.

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