THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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The breaking news in this our 103rd issue is the finding that acupuncture is highly effective in maintaining normal sinus rhythm after electrical cardioversion. A group of Italian researchers compared post-cardioversion effectiveness of amiodarone, acupuncture and sham-acupuncture in a group of lone afibbers with persistent AF. They found amiodarone and acupuncture about equally effective in maintaining NSR and both were twice as effective as sham-acupuncture, and above 50% more effective than no treatment. It seems to me that if acupuncture is effective in preventing recurrence after cardioversion of persistent afib, there is no reason why it would not also be effective in helping to extend the time interval between paroxysmal episodes. It certainly would seem worth a try, especially now that the exact location of the points to be stimulated has been published.

Also in this issue we report that a group of electrophysiologists from the Royal Melbourne Hospital found that the incidence of major complications associated with pulmonary vein isolation procedures is less than 1% among lone afibbers. Some other topics covered in this issue – low magnesium levels are closely related to the risk of sudden cardiac death, ranolazine may be an effective pill-in-the-pocket approach for heart disease patients who cannot use flecainide or propafenone, right atrial flutter ablation may unmask atrial fibrillation, and combining warfarin with antiplatelet agents can increase bleeding risk by up to 300%.

Finally, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at http://www.afibbers.org/vitamins.htm - your continuing support is truly appreciated.

Wishing you good health and lots of NSR,

Hans

Highlights

Ablation news from Australia

MELBOURNE, AUSTRALIA. Several studies have reported a major complication rate of 4 – 6 % associated with pulmonary vein isolation (PVI) procedures for the purpose of curing atrial fibrillation. Now a group of electrophysiologists from the Royal Melbourne Hospital reports that the incidence of major complications associated with PVI procedures is less than 1% among lone afibbers.

Their study covered 500 consecutive procedures involving 424 patients during the period July 2006 to September 2009 (repeat rate of 15%). The average age of patients was 55 years (44 to 66 years), 79% were male, and 95% were lone afibbers (80% paroxysmal, 20% persistent). All patients were at low risk for stroke with 64% having a $CHADS_2$ score of zero and 28% having a score of 1 (primarily due to hypertension). After checking for thrombi in the left atrium and left atrial appendage (none were found) all patients underwent a standard pulmonary vein antrum isolation (PVAI) procedure using the CARTO mapping system, a circular mapping catheter, and further guidance by transesophageal echocardiography (TEE) and selective angiography.

All procedures were carried out under general anesthesia by one of four electrophysiologists.

Complete isolation (after a 30-minute waiting period) was observed in 99% of the targeted veins. Additional ablations (linear ablation or ablation of fractionated electrograms) were performed in 24% of patients – the majority of whom had persistent AF. Antiarrhythmic therapy was restarted immediately after the procedure and continued for 3 months. All patients had a minimum hospital stay of 2 nights post-procedure.

The incidence of major procedure-related complications was 0.8% consisting of two cases of esophageal hematoma caused by the TEE probe, a pharyngeal trauma also related to the TEE probe, and one case of retroperitoneal hematoma requiring blood transfusion. There were no cases of death, stroke, transient ischemic attack (TIA), tamponade, atrioesophageal fistula, or pulmonary vein stenosis (screening was performed at 3, 6, 9 and 12 months and at least every 6 months thereafter). The authors of the study conclude that PVAI procedures can be performed safely in AF patients without structural heart disease.

Lee, G, et al. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation. **Journal of Cardiovascular Electrophysiology**, *August 19, 2010 [Epub ahead of print]*

Editor's comment: The findings of this study add to the evidence that PVI procedures are very safe for lone afibbers. It is unfortunate that the study did not include data on long-term success rates as these are generally not predictable from the immediate success rates (complete PVI at time of procedure).

Another reason to keep one's magnesium status up

MINNEAPOLIS, MINNESOTA. Sudden cardiac death (SCD) accounts for over half of all deaths from cardiovascular disease in the United States. As the name implies, SCD happens without warning and mostly occurs among people without known cardiovascular disease. However, hypertension, diabetes, obesity, and a family history of myocardial infarction (heart attack) are known to increase the risk of SCD. Now a group of researchers from four American and one Japanese university reports that a high serum magnesium level substantially reduces the risk of SCD.

Their study involved 7,887 women and 6,345 men between the ages of 45 and 64 years when enrolled in the study during the period 1987 – 1989. The baseline examination included a measurement of serum magnesium level (normal range of 1.3 – 2.1 mEq/L or 0.7 – 1.05 mmol/L). During a 12-year follow-up period (173,000 person-years), 264 cases (0.15%/year) of SCD were observed. Among participants with serum magnesium level at 1.5 mEq/L or less (lowest quartile) the incidence was 2.41 events/1000 person-years, while among those with a serum level at 1.75 mEq/L or higher (highest quartile) the incidence was 0.98/1000 person-years. In other words, the incidence of SCD was 55% lower among participants in the highest quartile of serum magnesium level. The risk reduction dropped to 38% after adjusting for numerous variables that could possibly affect the correlation (cholesterol level, QT interval, serum potassium level, physical activity, smoking status, alcohol intake, education level, age, diabetes, hypertension and use of diuretics).

The researchers make several other interesting observations:

- There was no correlation between dietary magnesium intake as measured by a food frequency questionnaire and SCD.
- A higher magnesium levels was associated with a 5% increase in LDL cholesterol, a 3% increase in HDL cholesterol, and an 18% drop in triglycerides.
- A lower magnesium level was associated with smoking, high systolic blood pressure, hypertension, diabetes, lower education level, and being female or African-American.
- Using non-potassium-sparing diuretics for hypertension increases the risk of SCD.
- Diuretics, while being useful in reducing blood pressure, also lead to excessive magnesium loss through urinary excretion.

The researchers conclude that if the association between low serum magnesium levels and risk of SCD is confirmed in other studies, then clinical trials

evaluating the impact of magnesium supplementation on SCD should be considered.

Peacock, JM, et al. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. **American Heart Journal**, *Vol. 160, No. 3, September 2010, pp. 464-70*

Editor's comment: Just one more reason to ensure an adequate daily intake of magnesium.

Changing pattern of drug therapy for AF

VANCOUVER, CANADA. Pharmaceutical drug therapy for atrial fibrillation is designed to either re-establish and maintain normal sinus rhythm (NSR) through the use of antiarrhythmic drugs (rhythm control), or to maintain a safe and comfortable ventricular rate (pulse rate) through the use of beta-blockers, calcium channel blockers or digoxin (rate control). Several trials have demonstrated that there is no significant difference in outcome (survival, stroke prevention, and quality of life) for the two protocols.

A group of Canadian researchers has investigated the changing patterns in pharmacological treatment of AF during the period 1991 to 2007. Their study included 1400 patients with new onset afib enrolled in the Canadian Registry of Atrial Fibrillation (CARAF). Among the highlights of their findings are:

- The proportion of patients receiving antiarrhythmic drugs (AADs) increased from 26.9% in 1991 to 42.4% in 1994, but then declined steadily to about 22% in 2007. Throughout the 1990s sotalol was the most prescribed AAD, peaking in 1993 at 27%. Subsequently its use declined steadily to 6% in 2007. Amiodarone prescriptions increased from 1.6% in 1991 to 17.9% in 2007. Propafenone was also quite popular in the 1990s peaking at 13.3% in 1995 and declining to about 2% in 2007. Flecainide use was low throughout the study period peaking at 2.0% in 2001. NOTE: The low use of flecainide and propafenone may indicate that most patients enrolled in CARAF had underlying heart disease and thus were not suitable candidates for therapy using these two Class 1C drugs. Quinidine was used by 9.5% of patients in 1995 but by 2005 it was no longer prescribed.

- The proportion of patients receiving rate control drugs exclusively decreased from a peak of 54.2% in 1991 to 34.1% in 1995. By 2000 the use of rate control started increasing again reaching 52.5% by 2007. In the early 1990s digoxin was the preferred rate control medication with 62.9% of patients using it. By 2007 this proportion had declined to 16.3%. The use of beta-blockers increased from 20.2% in 1991 to about 40% in 2007. Use of calcium channel blockers remained fairly steady over the 16-year period increasing from 14.3% in 1991 to 16.3% in 2007.

- About 50% of patients using rhythm control were also prescribed rate control drugs. Combinations of rate control drugs were frequently used with beta-blocker + digoxin being popular in the early years and beta-blockers + calcium channel blockers gaining popularity in later years.

- Patients receiving neither rhythm control nor rate control were significantly younger and were less likely to have hypertension or underlying heart disease. However, most of patients in this group (73%) had symptomatic afib.

- The CARAF Study confirmed other findings that paroxysmal afib tends to progress to the permanent variety. At first year of follow-up, 10-15% were in permanent afib as compared to 37% at the 10-year follow-up.

The authors make the following interesting comment about the reason for the decline in the use of AADs, "*It may be that the observed longitudinal decline in AAD use was merely a reflection of the acceptance of permanent AF by patients and their treating physicians, with a resultant shift toward a goal of ventricular rate control.*"

Andrade, JG, et al. Antiarrhythmic use from 1991 to 2007: Insights from the Canadian Registry of Atrial Fibrillation (CARAF I and II). **Heart Rhythm**, *Vol. 7, September 2010, pp. 1171-77*

Editor's comment: It is indeed gratifying to see the significant decrease in prescriptions for digoxin and sotalol. For **lone afibbers** at least these two drugs are ineffective and in the case of digoxin downright dangerous. The growing enthusiasm for rate control was largely fuelled by the results of the AFFIRM trial which found no significant difference in 5-year mortality between patients assigned to rhythm or rate control. Only 12% of the participants had lone

afib and to quote the authors, "*the results probably cannot be generalized to younger patients without risk factors for stroke (i.e. patients with primary, or "lone" atrial fibrillation), particularly those with paroxysmal atrial fibrillation.*"

Quite apart from the fact that the study is not particularly applicable to lone afibbers, I believe it had several serious flaws:

- The most "popular" drug used in the trial was digoxin. Over 70% of the people in the rate control group had used this drug at one time or another. Digoxin had been used by 54% of the participants in the rhythm control group as well. So as far as digoxin use is concerned, there was little difference between the two groups.
- Beta-blockers were used liberally in both groups as well – 68% in the rate control group and 50% in the rhythm control group.
- The main antiarrhythmic used was amiodarone (Cordarone). This drug was used by 63% of the patients in the rhythm control group and by 10% in the rate control group.
- The second most popular "antiarrhythmic" used in the rhythm control group was sotalol (Betapace) – this drug was used by 41% of patients despite the fact that it is well known that it does little, if anything, to maintain sinus rhythm, although it may help control the heart rate during an afib episode.
- Propafenone, flecainide and disopyramide had been used by only 4-15% of patients in the rhythm control group. It is impossible to say whether any of these drugs were beneficial or detrimental because of the way the data is reported.

The significant overlap in drug use between the two groups (especially in regards to digoxin) and the low usage of Class I antiarrhythmics detract somewhat from the value of the study.

New pill-in-the-pocket approach

WAUSAU, WISCONSIN. Flecainide and propafenone are both effective in terminating AF episodes when used on demand at the onset of an episode. Studies have shown that these drugs effectively convert 70-80% of patients with paroxysmal AF within 6 hours or less. Unfortunately, while **safe for lone afibbers** both of these Class 1C drugs can induce potentially fatal ventricular arrhythmias in patients with underlying heart disease. Thus a pill-in-the-pocket (PIP) approach is not currently available for this group of non-lone afibbers.

Four American electrophysiologists/cardiologists now report that ranolazine (Ranexa), a drug used in the treatment of angina pectoris may be an effective and safe PIP for afibbers with underlying heart disease. The four physicians compared notes in an uncontrolled, non-placebo-controlled retrospective chart review. They found that 25 of 35 patients (71%) who had been in AF for 3 to 48 hours converted to normal sinus rhythm within 6 hours of being administered 2000 mg of ranolazine orally. It is worth noting that 86% of the study participants had underlying structural heart disease. None of the patients experienced any cardiovascular side effects or worsening of afib symptoms.

The authors point out that ranolazine is safe for afibbers with underlying heart disease, has no pro-arrhythmic effects, and does not induce atrial flutter. It works to prevent afib by inhibiting abnormal late sodium channel current, increasing atrial refractoriness, and reducing pulmonary vein firing (PACs). The authors conclude that high-dose ranolazine is as effective as propafenone and flecainide, and that its conversion rate of 71% is substantially better than the 39% within 8 hours rate reported in the literature for placebo.

In an accompanying editorial two physicians from the Mayo Clinic point out that the study had a major flaw – it had no control group of individuals matched for age, gender, duration of afib, and concomitant illnesses. Nevertheless, they suggest that carefully controlled studies are warranted to establish "whether ranolazine is the promised drug or is just too good to be true."

Murdock, DK, et al. The conversion of paroxysmal or initial onset atrial fibrillation with oral ranolazine. **Journal of Atrial Fibrillation**, *Vol. 2, August 2010, pp. 705-10*

Gard, JJ and Asirvatham, SJ. Ranolazine for atrial fibrillation: Too good to be true? **Journal of Atrial Fibrillation**, *Vol. 2, August 2010, pp. 711-14*

Editor's comment: This new PIP drug looks promising and may be worth trying for afibbers with underlying heart disease. However, until more data is available lone afibbers should probably stick with propafenone or flecainide as these two drugs have undergone proper clinical trials to establish their effectiveness and safety.

Acupuncture – An effective antiarrhythmic?

MILAN, ITALY. Acupuncture is probably the world's oldest medical practice. It originated in China about 5000 years ago and was practiced in Egypt around 1250 BC. It was first described in detail in the *Nei Ching*, The Yellow Emperor's Classic of Internal Medicine published about 2500 years ago (500 BC). Acupuncture has been practiced in the United States for about 150 years and received a big boost in 1971 when *New York Times* reporter James Reston wrote about how doctors in China used needles to ease his pain after surgery. It is estimated that over 3 million Americans used acupuncture in 2006.

Articles in peer-reviewed medical journals describe the successful use of acupuncture to deal with conditions as varied as cocaine dependency, hiccups, and pregnancy-related pelvic pain. http://www.yourhealthbase.com/cgi-bin/htsearch?config=piwhbase&method=and&words=acupuncture. Thus it should not come as a surprise that Italian researchers have found acupuncture effective in preventing atrial fibrillation.

Their study, published in the prestigious *Journal of Cardiovascular Electrophysiology*, involved 80 patients with persistent AF who had just undergone successful cardioversion. The average age of the patients was 65 years and 70% were male. About two-thirds had accompanying hypertension and one-third had diabetes. All had normal left ventricular ejection fraction (52 – 61%), a left atrial diameter of 36 – 43 mm, but no heart disease or congestive heart failure. The average time since AF diagnosis was about 3 years.

Twenty-six of the study participants (33%) had been on amiodarone prior to their cardioversion and continued on this for the duration of the study (AMIO group). The remaining patients were randomly assigned to receive acupuncture (ACU group – 17 patients), sham acupuncture (ACU-sham group – 13 patients), or no follow-up treatment (CONTROL group – 24 patients).

Acupuncture Points

Acupuncture involves the insertion of sharp, thin needles at very specific points in the body. These points are located on meridians and channels believed to facilitate the movement of energy (Chi, Qi) throughout the body. The three specific points used in the Italian clinical trial are:

- **Neiguan (PC-6)** located on the pericardium channel about two finger's width above the crease of the wrist on the inner arm between the two tendons. The pericardium channel controls blood flow as well as pulse rate. Stimulation of the Neiguan point has been used to counteract palpitations and a sense of fullness in the chest. There is also evidence that it help restore autonomic nervous system balance.

- **Shenmen (HT-7)** is located on the heart meridian near the crease of the wrist on the side of the little finger (in the depression between the ulna and the pisiform bones). It is also called the Spirit Gate and stimulation helps calm anxiety, heart palpitations and irregular heart beat.

- **Xinshu (BL-15)** is located on the bladder meridian and can be found on the left side of the back near where the 5th rib joins the vertebrae. Stimulation of Xinshu has a modulating effect on the autonomic nervous system.

The ACU group and the ACU-sham group each attended 10 weekly acupuncture sessions. In the ACU group needles were placed in the Neiguan, Shenmen and Xinshu points (on both sides of the body), while the ACU-sham group's needles were placed in spots at least 2 cm from any known acupuncture point. During the following 12 months, afib recurred in 35 patients (44%). The recurrence rate for the four groups at 6 and 12 months are shown in the following table:

Recurrence Rate, %

Group	Treatment	6 months	12 months
AMIO	Amiodarone	18%	27%
ACU	Acupuncture	22%	35%
ACU-sham	Sham acupuncture	61%	69%
CONTROL	No treatment	50%	54%

There was no statistically significant difference between the recurrence rate in the AMIO and ACU groups. However, the recurrence rate was significantly higher in the CONTROL and ACU-sham groups.

The researchers point out that there is ample evidence that acupuncture is effective in treating both hypertension and supraventricular tachycardia. Acupuncture at the Neiguan and Xinshu points both help modulate and stabilize the autonomic nervous system, while stimulation of the Shenmen point has a calming and sedative effect on cardiac excitability. They conclude, "*acupuncture treatment prevents arrhythmic recurrence after cardioversion in patients with persistent AF. This minimally invasive procedure was safe and well tolerated.*"

Lomuscio, A, et al. Efficacy of acupuncture in preventing atrial fibrillation recurrences after electrical cardioversion. **Journal of Cardiovascular Electrophysiology**, *August 30, 2010 [Epub ahead of print]*

Editor's comment: The "official" discovery that acupuncture can help recurrence of afib after cardioversion is clearly very exciting. At least two afibbers have been helped very substantially by acupuncture and their stories can be found at:

http://www.afibbers.org/resources/journeys/Craig.pdf
http://www.afibbers.org/resources/journeys/Girskis.pdf

If acupuncture is effective in preventing recurrence after cardioversion of persistent afib, there is no reason why it would not also be effective in helping to extend the time interval between paroxysmal episodes. It certainly would seem worth a try, especially now that the exact location of the points to be stimulated has been published.

Flutter ablation may unmask AF

MUNCIE, INDIANA. Common atrial flutter (AFL) originates in the right atrium between the tricuspid valve and the *crista terminalis*. Because the location of the AFL-associated macroreentrant circuit is so well defined a catheter ablation to interrupt it is usually successful. However, as many as half of all patients ablated for AFL may later develop atrial fibrillation (AF) thought to be unmasked by eliminating the flutter. An obvious question is would it be desirable to combine the standard AFL ablation (cavotricuspid isthmus or CTI) ablation with a pulmonary vein isolation (PVI) procedure at the time of the initial flutter ablation?

A group of doctors from the Ball Memorial Hospital provides a preliminary answer to this question. Their clinical trial involved 48 patients with **lone** right atrial flutter. NOTE: In this case, **lone** means that no other cardiac arrhythmia was present. The average age of the patients was 55 years, very few (number not specified) had heart disease, but 60% had hypertension. Patients were randomly assigned to receive only a CTI ablation (25 patients) or a CTI ablation combined with a PVI procedure with additional lesions as required (23 patients). Total average procedure time for the CTI ablation was 84 minutes as compared to 239 minutes for the combined procedure. Fluoroscopy time was 8.2 minutes and 20.1 minutes respectively. All patients were anticoagulated for one month prior to the procedure and for two months following. All received a Class 1C antiarrhythmic drug (flecainide

or propafenone) for two months following their procedure and underwent 48-hour Holter monitoring every two months. Only four minor adverse events were observed – hematoma and mild pericardial effusion.

After a 16-month follow-up, 87% of the group that had undergone both CTI and PVI ablation were free of any arrhythmia without the use of medication. However, in the CTI ablation group only 44% were so lucky – 10 patients (36%) developed paroxysmal AF and 5 (20%) developed persistent AF during follow-up. The researchers conclude that adding PVI ablation to CTI ablation for **lone** atrial flutter provides better long-term freedom from arrhythmias than just performing the CTI ablation on its own.

Navarrete, A, et al. Ablation of atrial fibrillation at the time of cavotricuspid isthmus ablation in patients with atrial flutter without documented atrial fibrillation derives a better long-term benefit. **Journal of Cardiovascular Electrophysiology**, *July 19, 2010 [Epub ahead of print]*

Editor's comment: It is well established that undergoing just a CTI ablation in an attempt to cure afib, or afib coexisting with atrial flutter, is usually fruitless with a success rate somewhere between 5 and 10%. This study provides convincing evidence that even if a patient has only been diagnosed with atrial flutter, it would be better to combine the CTI ablation with a PVI procedure "right off the bat" rather than wait to see if the flutter ablation "unmasks" coexisting afib.

AF and angiotensin II receptor blockers

BAD NAUHEIM, GERMANY. There is substantial evidence that the renin-angiotensin-aldosterone system (RAAS) is involved in fibrosis formation and cardiac remodeling in atrial fibrillation (AF) patients. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) have been tested in clinical trials involving more than 50,000 AF patients and a significant reduction in afib severity has been demonstrated. It is, however, not clear why some patients benefit from taking ACE inhibitors or ARBs (from hereon designated as RASBs), while others do not.

A team of cardiologist at the Kerckhoff Heart Center in Germany now reports that AF burden and degree of left atrial enlargement are the main factors determining whether ACE inhibitor/ARB therapy will be beneficial. The goal of their study was to identify patients with AF and hypertension who may benefit from RASB therapy after a pulmonary vein isolation (PVI) procedure.

The study involved 284 patients with hypertension and AF (77% paroxysmal, 23% persistent) who had suffered from afib for an average of 5 years. The average age of the study participants was 61 years, 65% were male, and 15% had underlying heart disease. The German researchers divided the patients into two groups. The first group consisted of 167 patients with paroxysmal afib whose burden (number of episodes x duration) was less than 500 hours over a 3-month period (low-burden AF). The second group consisted of 67 patients with persistent afib (episodes lasting 7 days or longer, but amenable to cardioversion) and 50 patients whose afib burden exceeded 500 hours over a 3-month period (high-burden AF). Participants of the low-burden group had a significantly smaller left atrium and a better left ventricular ejection fraction at baseline (prior to the PVI procedure) than did those of the high-burden group.

Patients underwent a circumferential radiofrequency catheter ablation (69%) or a cryoballoon procedure (31%). Irrespective of the energy source used, all patients who failed to achieve sinus rhythm after isolation of the pulmonary veins underwent additional substrate modification with a 4-mm irrigated radiofrequency-powered catheter. After a 3-month blanking period all patients were evaluated with 7-day Holter monitoring every 3 months for the first year and every 6 months thereafter.

The endpoint of the study was defined as first documented AF recurrence lasting more than 30 seconds (following the 3-month blanking period). After a median follow-up of 13.8 months, 52% of study participants were free of AF. The main variables affecting afib status were AF burden, left atrial area, and whether or not the patients had been administered RASBs. Among low-burden afibbers 64% were free of afib at the end of follow-up as compared to only 36% in the high-burden group. A left atrial area (normalized) of less than 11.5 cm^2 was associated with a 59% recurrence-free rate, while a left atrial area of 11.5 cm^2 or greater was associated with a 36% recurrence-free rate. The administration of RASBs was associated with a 57% recurrence-free rate vs. 40% for patients whose hypertension was controlled with anti-

hypertensive medications other than ACE inhibitors and ARBs.

Multivariable analysis showed that patients with high-burden AF had a two-fold increased risk of AF recurrence as compared to the low-burden group. Patients with an enlarged left atrium (area equal to or greater than 11.5 cm^2) had a 92% increased risk and those not taking RASBs had a 66% increased risk. However, the beneficial effect of RASB administration was limited to the low-burden group. RASB administration was also significantly more effective in patients with a non-enlarged left atrium.

The German researchers speculate that *the greatest benefit of ACE inhibitors or ARBs for the prevention of AF might be seen in trials of primary prevention (i.e. prevention of new-onset AF), because these drugs might prevent, but not reverse, the development of the atrial electrical and structural remodeling that is required to provide the substrate for AF*. They suggest that RASB therapy should be administered to all hypertensive patients after a first diagnosis of atrial fibrillation.

Berkowitsch, A, et al. Therapy with renin-angiotensin system blockers after pulmonary vein isolation in patients with atrial fibrillation. **PACE**, *Vol. 33, September 2010, pp. 1101-11*

Editor's comment: Although this retrospective study involved afibbers with hypertension, 85% of participants did have lone atrial fibrillation (no underlying heart disease). Thus it is conceivable that RASB therapy may help prevent AF episodes in low-burden afibbers both prior to and subsequent to a PVI procedure. It would also seem reasonable for lone afibbers with hypertension to use an ACE inhibitor or ARB to control their blood pressure rather than diuretics, beta-blockers or calcium channel blockers. Finally, it would appear that a PVI procedure should be considered before the afib burden exceeds 500 hours per 3 months and before the left atrium becomes overly enlarged.

Anticoagulation – Dangerous combinations

COPENHAGEN, DENMARK. Atrial fibrillation patients with risk factors for ischemic stroke are usually prescribed aspirin or warfarin. In some cases, particularly in patients with coexisting cardiovascular disease, an antiplatelet agent such as aspirin or clopidogrel are added to warfarin in the belief that this will further reduce stroke risk. Danish researchers now report that the practice of combining antiplatelet and anticoagulation therapy in the same patients is associated with a substantially higher risk of fatal or non-fatal internal bleeding.

Their study included 118,606 patients who were discharged from hospital between January 1, 1997 and December 31, 2006 with a diagnosis of atrial fibrillation (AF). The mean age of the patients was 74 years and 52% were male. Many had comorbidities such as hypertension (16%), heart failure (18%) or ischemic heart disease (16%), while 7% had suffered a previous ischemic stroke. About 77% were taking antiarrhythmic drugs and 27% were being treated with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor antagonists. About 70% of the patients were discharged with a prescription for antiplatelet agents and/or warfarin. The pattern of prescriptions was as follows:

- Warfarin – 42.9%
- Aspirin – 40.1%
- Clopidogrel – 3.1%
- Clopidogrel + aspirin – 2.4%
- Warfarin + aspirin – 15.5%
- Warfarin + clopidogrel – 1.2%
- Warfarin + aspirin + clopidogrel – 1.1%

Patients treated only with aspirin were older and more often female than were those in the other treatment groups. During the 10-year follow-up period, 1381 patients (1.2%) experienced a fatal bleeding, while 12,191 (10.3%) were hospitalized as the result of a non-fatal internal bleeding. Using warfarin as a reference point, aspirin-treated patients had a 4% reduced risk of experiencing a bleeding event but all combination treatments were associated with a substantial increase in risk.

- Clopidogrel monotherapy – 45% increased risk
- Aspirin + clopidogrel – 91% increased risk
- Aspirin + warfarin – 75% increased risk
- Clopidogrel + warfarin – 257% increased risk
- Clopidogrel + aspirin + warfarin – 303% increased risk

The use of clopidogrel either alone or in combination was primarily associated with an increased risk of gastrointestinal bleeding. Patients

who had experienced a non-fatal bleeding event during therapy had a 145% increased risk of dying during the follow-up period. It is also worth noting that the 3.9% annual bleeding incidence observed in this "real world" study is substantially higher than that found in closely controlled clinical trials. Also, the bleeding incidence during the first year of warfarin therapy is 7% among elderly patients. Perhaps most surprising, there was no indication that combining warfarin with an antiplatelet agent (aspirin, clopidogrel or both) reduced the risk of ischemic stroke.

The article concludes with the following note from the editor, "*They* [the Danish researchers] *find that adding clopidogrel or aspirin to warfarin monotherapy greatly increases the fatal and non-fatal bleeding risk while showing no benefit to prevention of ischemic stroke."*

Hansen, ML, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. **Archives of Internal Medicine**, *Vol. 170, No. 16, September 13, 2010, pp. 1433-41*

Editor's comment: This study clearly shows that there is no advantage and much potential risk in using combined antiplatelet/anticoagulation therapy in atrial fibrillation patients needing stroke prevention therapy. It is unfortunate that the authors did not include actual data on the incidence of stroke in the different treatment groups and compared it to a group receiving no treatment.

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