Much research is devoted to determining the real success rate of pulmonary vein ablation. It is now clear that the success rate for persistent and permanent afib is lower than that for paroxysmal afib and that achieving a satisfactory cure requires considerably greater skill than is needed for a PVI involving a paroxysmal afibber.

It is also becoming clear that success rates are highly dependent on the protocol used to measure them. They are significantly higher when counting only episodes reported by the patient than when counting all episodes recorded on a Holter monitor or a transtelephonic ECG recorder. German researchers have found that more than half the episodes encountered in the 6-month period following an ablation are asymptomatic, and a team of British and Irish researchers concluded that more than 90% of all afib episodes recorded in a group of older paroxysmal afibbers were completely symptomless. While these findings are disturbing, they are probably not of great concern to lone afibbers with no risk factors for stroke since this group has been found to have an incidence of ischemic stroke below that of the general population.

Also in this issue we report on a warning regarding the combination of taking paroxetine along with digoxin, warfarin bleeding risk, the long-term outcome of PVI for persistent afib, and the questionable effectiveness of electrical cardioversion.

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Yours in NSR,
Hans

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Atrial fibrillation: The genetic component

REYKJAVIK, ICELAND. Iceland is unique in the fact that it has a genealogy database containing records for all 284,000 living Icelanders and a large proportion of their ancestors as far back as 930 AD. NOTE: According to studies based on Y-chromosome and mitochondrial polymorphism, it appears that 75% of all male Icelanders originally came from Norway, while 66% of all female Icelanders are of Celtic origin – seems that the Vikings went far afield for their wives!

A team of researchers from the University Hospital in Reykjavik and the National Institutes of Health in the US has just completed a study using the genealogy database and hospital records for 5269 patients admitted with atrial fibrillation during the period 1987-2003. The aim of the study was to determine the inherited risk of developing AF.

The researchers conclude that Icelanders with a first-degree relative with afib have a 77% (RR=1.77) greater risk of developing afib than do members of
the general population. The risk declines the further the afflicted family member is removed. Thus, an Icelander with a third-degree relative diagnosed with afib has an 18% increase in risk. The heritability factor was particularly pronounced in afibbers who were diagnosed prior to the age of 60 years. Their immediate offspring were almost 5 times (RR=4.67) more likely to develop AF than were matched members of the general population. The researchers speculate that this may indicate that a genetic connection is much more common among lone afibbers than among afibbers with heart disease.


**Editor’s comment:** One of the early LAF surveys found that 43% of the 100 lone afibbers responding had a close relative who also suffered from atrial fibrillation. Either the mother or the father was “the carrier” for 23% of the 100 respondents.

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**Digoxin and paroxetine do not mix**

HIROSAMI, JAPAN. Japanese physicians report a case of a 68-year-old woman who developed severe digoxin (digitalis) intoxication after starting on paroxetine (Paxil) for depression, insomnia, and difficulty concentrating. The patients had suffered from atrial fibrillation for 2 years and, during this time, had been treated with 0.25 mg digoxin and 1 mg warfarin daily. Two days after beginning on 20 mg/day of paroxetine she experienced nausea, vomiting, and dizziness. Delirium with visual hallucinations followed on day 4 and by day 8 she could no longer eat or walk. On day 9 the doctors suspected digitalis intoxication (serum digitalis concentration was 5.2 ng/mL compared to the normal range of 0.5-2.0 ng/mL). An ECG showed numerous PVCs and complete A-V block. On day 10 all medications were withdrawn resulting in the patient going into bradycardia as a rebound effect of discontinuing digoxin. On day 19 digoxin and warfarin (but not paroxetine) were restarted. The patient remained depressed, developed pneumonia, and died in hospital 3 months later.

The physicians speculate that paroxetine and digoxin are metabolized via the same pathway and that the competition leads to digitalis intoxication. They suggest that citalopram (Celexa) or venlafaxine (Effexor) may be better choices for an antidepressant to be co-administered with digoxin.


**Editor’s comment:** A lone afibber should NEVER ever accept a prescription for digoxin. There is absolutely no evidence that it is beneficial and substantial evidence that it is likely to materially worsen lone AF.

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**Optimizing algorithms for ICDs**

BONN, GERMANY. Highly sophisticated, programmable pacemakers (ICDs) are finding increasing application in the management of paroxysmal atrial fibrillation. Their programs (algorithms) are based on the observation that most afib episodes are preceded by an increase in the number of premature atrial complexes (PACs). If the heart rate is increased by pacing when an increase in PACs is detected an afib episode can often be avoided.

A team of clinicians from 84 heart centers in 11 European countries has just reported the results of a study aimed at determining if different pacing algorithms would have different effects in a group of 126 paroxysmal afibbers who required a pacemaker implant because their normal heart rate was excessively low. After pacemaker implantation the recipients spent at least 6 weeks as a “run-in” period and then entered a 3-month diagnostic phase. During this phase the pacemaker was in normal dual-chamber pacing mode with the lower heart rate limit set to 60 beats/minute. The afib prevention algorithms were disabled. The purpose of the diagnostic phase was to determine each participant’s baseline afib burden (time spent in afib per day) and to separate the participants into two groups. Group 1 (Trigger Group) consisted of 73 afibbers whose episodes were triggered by a sequence of more than 2 PACs/minute. Group 2 (Substrate Group) consisted of 53 afibbers whose episodes did not seem to be related to increased PACs (less than 2 PACs/minute). The researchers speculate that the members of the Substrate Group
were more likely to have a damaged atria and therefore not be solely dependent on increased PAC activity as the initiator for an afib episode.

After establishing the baseline afib burden, the study participants entered the therapy phase during which their ICD was programmed either for continuous overdrive pacing (Substrate Group) or for PAC suppression pacing (Trigger Group). PAC suppression pacing involves raising the heart rate by 15 bpm upon detection of a PAC and maintaining the elevated heart rate for 600 beats before returning to non-pacing.

The researchers found that the median afib burden in the Trigger Group was reduced from 2.06 hours a day in the diagnostic phase to 1.49 hours a day in the therapy phase for a relative reduction of 28%. About 39% of participants reduced their afib burden by 70-96%. This “super response” was significantly more common in the Trigger Group. The researchers conclude that selecting the PAC suppression algorithm may benefit a group of afibbers whose episodes are primarily initiated by an increase in PAC activity. No reduction in afib burden was observed in the Substrate Group with the use of continuous, overdrive pacing.


ST. LOUIS, MISSOURI. Many lone afibbers are counseled to take warfarin (Coumadin) although there is no evidence that doing so will reduce the risk of ischemic stroke (caused by a blood clot) for afibbers who do not have specific risk factors for stroke, more specifically, coronary artery disease, congestive heart failure, rheumatic heart disease, hypertension, advanced age, diabetes, a prior history of stroke or heart attack, or the presence of prosthetic heart valves.

Unfortunately, there is considerable evidence that taking warfarin is associated with a significantly increased risk of internal bleeding and hemorrhagic stroke (stroke caused by a burst blood vessel). Researchers at the Washington University School of Medicine have now developed a rating scheme for predicting the risk of internal bleeding for atrial fibrillation patients taking warfarin. They determined risk factors for warfarin-related bleeding incidents by studying the records of 1604 afibbers released from hospital on warfarin. They assigned one point to each of the following factors:

- Liver or kidney disease
- Alcohol abuse
- Cancer
- Advanced age (greater than 75 years)
- Reduced platelet count or function
- Uncontrolled hypertension
- Anemia
- Unfavourable genetic factors
- Excessive risk of falling
- Prior stroke

Patients who had already suffered an internal bleed were given an extra two points. Using this scheme (HEMORR\_HAGES) the researchers predicted the following annual incidence of bleeding requiring hospitalization for afibbers on warfarin:

<table>
<thead>
<tr>
<th># of Risk Factors</th>
<th>% Risk of Bleeding/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>10.4</td>
</tr>
<tr>
<td>5 or more</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Most of the bleeds (67.3%) were gastrointestinal hemorrhages, 15.3% were hemorrhagic strokes, and the remaining 17.3% were in other locations. The seriousness of the bleeds can be judged from the fact that 21.6% of the patients admitted for warfarin-induced bleeding died within 30 days. This is, no doubt, related to the fact that a hemorrhagic stroke is far more likely to be lethal than an ischemic one and that a serious gastrointestinal bleed can quickly become fatal.

The researchers conclude that their new rating scheme, HEMORR\_HAGES, will be useful in assisting doctors and patients in judging the advisability of warfarin therapy in atrial fibrillation patients.


Editor’s comment: This study is clearly an important step forward in determining the risk/benefit ratio of warfarin therapy in afibbers. It is particularly illuminating to compare the risk for ischemic stroke according to the CHAD2 score and the Kaiser Permanente Study with the risk of major bleeding according to the HEMORR2HAGES scheme.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk of Ischemic Stroke, %/year</th>
<th>Risk of Major Bleed, %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension or age over 75 yrs</td>
<td>2.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypertension + age over 75 yrs</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Prior bleed</td>
<td>1.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

[3] Average of two estimates weighed by number of patients in studies.

Looking at the above comparison, it is clear that most afibbers with just one or two risk factors for ischemic stroke would be exposed to a greater risk of a serious adverse event by taking warfarin than by not taking it. It is abundantly clear that warfarin has no place in the treatment of afibbers with no risk factors, but a case can probably be made for recommending warfarin for afibbers who have already experienced an ischemic stroke. It is also important to remember that the HEMORR2HAGES study found that 21.6% of patients admitted to hospital with warfarin-induced bleeding died within 30 days. In contrast, the mortality associated with an ischemic stroke varies between 5 and 25% depending on the nature of the treatment and how quickly it is received.

Long-term outcome of PVI for persistent AF

MESTRE, ITALY. Emanuele Bertaglia and colleagues at the Ospedale Civile di Mirano report on their follow-up of 74 persistent afibbers who had undergone circumferential pulmonary vein ablation (CPVA or Pappone method) for persistent AF (afib episodes lasting longer than 7 days). The average age of the patients was 61.5 years (49-78), 76% were men, average afib duration was 4.4 years (1-17), and all had tried at least 2 antiarrhythmic drugs (3.1 on average) with no success.

The ablation was performed using the CARTO anatomical mapping system and a cooled 3.5 mm Navistar catheter. Total procedure time averaged about 3.5 hours with a fluoroscopy time of about 28 minutes. All patients had their pulmonary veins isolated – 78% also had the right isthmus ablated (to prevent right atrial flutter), and 67% received an ablation line connecting the mitral valve to the left inferior PV (left isthmus). All patients continued on antiarrhythmic drugs for the first 7 months and were then taken off the drug or continued based on their response.

After a mean follow-up of 20 months, 70% of the patients were still in normal sinus rhythm (NSR) and were deemed to have been successfully treated. NOTE: 63% of these patients were either on amiodarone (18 patients) or Class IC drugs (15 patients). Of the 22 patients (30%) who relapsed into afib within the first 2 years, 19 did so within the first 12 months after the ablation procedure, while only 3 did so after 12 months. The researchers conclude that not having a relapse within the first 12 months and having suffered from persistent afib for less than 7 years are strong predictors of a successful outcome.

The researchers point out that the necessity of continuing antiarrhythmic drugs in this group of
persistent afibbers was significantly higher than normally experienced among ablated paroxysmal afibbers. They make this very interesting statement concerning this finding, “It could be explained by the fact that, whereas in patients with paroxysmal AF elimination of triggers is often enough to eradicate the arrhythmia, in patients with persistent AF the role of atrial electrical and structural remodeling is predominant over triggers. So, the modifications of anatomical and electrical substrate induced by circumferential ablation more often need to be aided by the continuation of antiarrhythmic drugs.”


Factors affecting late recurrence of AF following a PVI

TAIPEI, TAIWAN. It is barely 8 years since Professor Haissaguerre in Bordeaux first attempted pulmonary vein isolation (PVI) and only in the last 4 or 5 years have PVIs become widely accepted and performed. So, it is not too surprising that data regarding the ultimate long-term success of the procedure are only just emerging. Unfortunately, the news is not as encouraging as could be hoped for. Some studies have found recurrence rates as high as 50% after a seemingly successful PVI.

Researchers at the Taipei Medical University School of Medicine found a recurrence rate of 35% among 293 afibbers having undergone a seemingly successful first ablation. Of the 104 patients who experienced a late recurrence, 81 (78%) did so within one year after their PVI, while the remaining 23 (22%) did so more than one year post-procedure. Fifty of the 104 recurrence patients underwent a second ablation procedure during which careful electrophysiological (EP) measurements were repeated. Twelve of the patients (Group 1) had experienced their recurrence between 13 and 39 months (average of 26 months) after their PVI, while the remaining 38 (Group 2) had experienced their first afib episode post-ablation within 1 to 12 months (average of 3 months). The EP studies yielded the following intriguing information:

- At the baseline EP study (prior to the first ablation) Group 1 patients had fewer AF foci originating from the pulmonary veins than did those in Group 2 (67% vs 92%), but substantially more foci in the right atrium (50% vs 13%).
- At the repeat EP study (prior to the second ablation) Group 1 patients again had a lower incidence of pulmonary vein foci (50% vs 79%) and indeed of total left atrium foci (50% vs 97%). Most remarkably, the incidence of right atrium foci in Group 1 patients was 67% vs only 3% in Group 2.
- The majority of initiating foci (65%) in both groups were spots that had already been targeted in the first ablation, thus indicating that conductivity had been regained. The phenomenon of recovered conductivity was particularly pronounced at the pulmonary veins where 100% of foci found in the study preceding the second ablation had already been “burned” during the initial ablation.
- After an average of 2 years (7-35 months) after the second ablation, 83% of group 1 patients were free of afib without the use of antiarrhythmics, while the remaining 17% were able to control their condition with the use of previously ineffective drugs. In Group 2 (13-61 months after second ablation) 74% were afib-free without drugs, while the remaining 26% achieved satisfactory control with antiarrhythmics.

The researchers conclude that right atrial foci play an important role in the very late (more than 1 year) recurrence of afib, while regained conductivity in pulmonary vein foci are most important in so far as late (less than 1 year, but more than 1 month) recurrence is concerned.


Lloyd, MS and Langberg, JJ. Recurrences of atrial fibrillation after ablation: When will this hydra meet its Hercules? Journal of Cardiovascular Electrophysiology, Vol. 17, March 2006, pp. 236-37
Effectiveness of electrical cardioversion

ROCHESTER, MINNESOTA. Patients with persistent atrial flutter or fibrillation often undergo direct-current cardioversion (DCCV) in an attempt to bring the heart back into normal sinus rhythm (NSR). Dr. Paul Friedman and colleagues at the Mayo Clinic have just released the results of a study aimed at determining just how effective DCCV really is. The study included 351 patients with atrial fibrillation (179 with a first episode) and 126 patients with atrial flutter (78 with a first episode). The patients were all over the age of 60 years and most had hypertension (68%), while 49% had moderate to severe atrial enlargement. Most were on one or more medications including 29% on digoxin, 92% on warfarin, and 53% on ACE inhibitors or angiotensin-converting enzyme inhibitors.

The study participants underwent standard DCCV and were then followed-up for a year. At the one-year follow-up 63% of the patients who had been cardioverted after a first atrial flutter episode remained in NSR. However, only 33% of flutter patients with recurrent episodes remained in NSR.

The results for afibbers were even worse. Only 30% of patients in the new-onset afib group and 35% in the recurrent group were still in NSR after a year. It is interesting that not all atrial flutter patients relapsed into atrial flutter. In patients with recurrent atrial flutter, 39% relapsed into atrial fibrillation. AF patients, on the other hand, almost always (92-95% of cases) relapsed back into atrial fibrillation rather than into atrial flutter.


Editor's comment: Electrical cardioversion is clearly not very effective for the general afib population and there is no evidence that it is more effective for lone afibbers. However, there is some evidence that effectiveness increases if used together with antiarrhythmic drugs.

More evidence of asymptomatic AF episodes

HAMBURG, GERMANY. There is increasing recognition that even a seemingly successful pulmonary vein isolation (PVI) may not keep the patient in continuous normal sinus rhythm (NSR) when asymptomatic (silent) AF episodes are included in the evaluation of success.

German researchers recently reported on a study of 80 highly symptomatic, paroxysmal afibbers who had undergone a first-time PVI (segmental ostial ablation). Only 10% of the afibbers had coronary artery disease. After a seemingly successful ablation involving complete entrance and exit block of all pulmonary veins and bidirectional right atrial isthmus block (flutter ablation), the patients were provided with a transtelephonic ECG recorder for use during the 6 months following the ablation. They were instructed to transmit a 1-minute recording once a day as well as recordings whenever they felt symptoms that could be afib. They were also instructed to specify their symptoms by telephone.

A total of 6835 transtelephonic recordings were gathered and analyzed over the 6-month period. NSR was observed in 79.5% of the recordings with the remaining showing afib. Only 28% of participants showed continuous NSR during the entire 6-month study period. Seventy-two per cent of participants experienced an episode during the first month; however, about half of them were afib-free after 3 months. Thus, the total number of patients in NSR after 3 months was 52 or 65%. After 6 months, the success rate had declined to 61% and 23% of the patients underwent a second ablation.

Ninety per cent of patients who were in NSR reported being so, while 10% reported symptoms, predominantly palpitation (73%), tachycardia (13%), breathing difficulties (10%), and chest pain (4%). Conversely, when patients actually were in afib (as per recordings) only 46% of them reported symptoms, while the remaining 54% reported no symptoms. The most commonly reported symptoms were palpitation (60%), tachycardia (31%), breathing difficulties (5%), and chest pain (3%). The percentage of asymptomatic episodes increased from the first month after PVI (43.5%) to the 2nd to 6th month (57.5%). This confirms earlier reports that the preponderance of asymptomatic episodes tends to increase over time.
The researchers conclude that success of a PVI cannot be accurately judged by just considering patients with symptoms since more than half of all episodes are likely to be entirely symptomless (asymptomatic). This clearly has significant implications as far as anticoagulation and drug treatment is concerned.


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**European Cardiac Arrhythmia Society**

2nd Annual Congress

Marseille, France, April 2-4, 2006

Abstracts published in *PACE*, Vol. 29, April 2006, Supplement 1

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**Irrigated ablation catheter superior**

A team of American and Italian researchers has compared the safety and efficiency of the standard 8 mm radiofrequency ablation catheter and an open-tip, irrigated (with saline solution) catheter (*Celsius ThermoCool* diagnostic ablation catheter) in the performance of pulmonary vein isolation (PVI). Sixty-two afib patients were involved in the trial and complete isolation was achieved in all of them regardless of catheter used. However, radiation exposure (average fluoroscopy time) was significantly lower in the *ThermoCool* group (26 vs 39 minutes) and procedure time (total time catheters are present in left atrium) was also considerably lower in the *ThermoCool* group (60 vs 86 minutes). The team concludes that open-tip, irrigated catheters can safely be used for PVI procedures and that their use minimizes radiation exposure and procedure time.

*Abstract #7*, p. S4

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**Haissaguerre vs Pappone method**

Cardiologists at the German Heart Center in Munich have compared the outcome of ablations performed according to the Haissaguerre protocol (segmental pulmonary vein isolation or PVI) and the Pappone protocol (circumferential pulmonary vein ablation or CPVA). One hundred consecutive afib patients with a mean age of 58 years were randomized to undergo PVI (guided by electrophysiological measurements) or CPVA (guided by anatomical imaging). If afib recurred within a 12-month period following the initial procedure, a repeat procedure was performed using the same protocol as used in the initial one. Repeat ablations were required in 12 of the 50 PVI patients (24%) and in 22 of the 50 CPVA patients (44%). After repeat ablation 10 out of 12 patients in the PVI group (83%) were in stable sinus rhythm as compared to only 6 out of 22 (27%) in the CPVA group. The majority (92%) of patients in the PVI group needed their repeat ablation because of recurrence of atrial fibrillation (AF). In the CPVA group, however, only 41% were re-ablated solely for AF, while the remaining 59% developed left atrial flutter as a result of the first procedure and had to undergo ablation for that as well.

*Abstract #8*, p. S4

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**Symptoms and afib**

There is growing awareness that many afib episodes occur without the patient being aware of them, ie. they are completely asymptomatic. A team of British and Irish researchers has just completed a study comparing Holter monitor recordings with symptom diaries maintained by patients. The study involved 41 older afibbers (average age of 71 years) with symptomatic paroxysmal AF. The patients documented time and duration of their symptoms and this was correlated with Holter readings for a total of 1960 person-days. Overall, 33 symptomatic episodes (7%) were documented accurately by both patients and Holter recordings, 194 episodes (4%) were documented by patients, but did not show up on the Holter, and the remaining 4274 episodes (89%) recorded on the Holter had not been recorded by the patients. In other words, 92.8% of recorded episodes had been asymptomatic. The researchers suggest that the reported efficacy of drugs and other interventions should be taken with “a grain of salt” if strictly based on symptomatic episodes reported by patients.

*Abstract #33*, p. S17
Magnesium helps control afib
Canadian researchers have done a meta-analysis of studies dealing with the benefits of intravenous administration of magnesium in the acute treatment of atrial fibrillation. They found that effective rate control (reduction in heart rate to below 100 bpm) and/or conversion to normal sinus rhythm was achieved in 84% of patients given magnesium as compared to 53% given a placebo. Seven trials used calcium channel blockers or placebo as controls. In these trials 69% of patients in the magnesium group experienced relief as compared to 53% in the control group. The researchers conclude that intravenous magnesium is an effective and safe strategy for the acute treatment of afib.
Abstract #36, p. S19

Inflammation and early recurrence of post-ablation AF
There is some speculation that inflammation and edema caused by a pulmonary vein isolation (PVI) procedure may precipitate early recurrence of afib. Researchers at the Cleveland Clinic now report that treatment with a powerful anti-inflammatory (60 mg prednisone on day of procedure followed by methylprednisolone for 6 days) has no effect on the early recurrence of afib after an ablation. The only variable showing a significant association with early recurrence was left atrial size with a larger size predicting an increased risk of recurrence.
Abstract #38, p. S20

Bepridil for persistent afib
Japanese cardiologists have evaluated the short-acting calcium channel blocker bepridil (Vascor) in a group of afibbers with the persistent variety (episodes lasting longer than 7 days and requiring cardioversion to restore sinus rhythm). The group consisted of 159 patients with an average age of 58 years (89% male). Participants were given 100-200 mg/day of bepridil and followed for an average of 16 months. In 55% of patients, normal sinus rhythm (NSR) was established without cardioversion within 2.1 months of starting the drug and 85% of these patients remained afib-free during follow-up. Thirty-one patients who failed to spontaneously convert to NSR underwent direct current cardioversion. This restored NSR in all patients and 58% of them maintained NSR for an average of 20 months. The cardiologists conclude that bepridil is safe and useful for maintaining sinus rhythm in patients with persistent afib.
Abstract #119, p. S59