Welcome to our summer issue. There is increasing evidence and a slowly building consensus that the increased stroke risk associated with atrial fibrillation is due, not to AF as such, but rather to the comorbid conditions (atherosclerosis, heart failure, diabetes, etc) that accompany it, in most cases. Researchers at the Mayo Clinic recently made the following statement:

Our long-term data suggest that the increased risk of stroke in atrial fibrillation is due to ‘the company it keeps’.

In other words, lone atrial fibrillation is not a risk factor for stroke. The Mayo Clinic researchers also made this conclusion, which should warm the heart of all lone afibbers:

After more than 30 years of follow-up of our rigorously defined cohort, findings confirm that overall survival is not affected adversely by lone atrial fibrillation.

Also in this issue, we report that magnesium infusions are safe and effective in achieving rate and rhythm control during an acute AF episode. The success of cardioversion may be improved by reducing systemic inflammation prior to the procedure. Amiodarone may not be as effective as generally assumed and comes with the potential for serious adverse effects. Folic acid supplementation is effective in reducing the risk of stroke.

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 a safe and happy summer with lots of NSR,

Hans

## Highlights

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## Cardioversion success and inflammation

OSLO, NORWAY. Electrical cardioversion is the standard treatment for persistent afib episodes that do not terminate on their own. Unfortunately, it is not very effective with more than half of patients having another afib episode within a few months of conversion. There is some evidence that treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) help prevent episodes in atrial fibrillation patients with hypertension or left ventricular dysfunction.

Based on this observation Norwegian researchers decided to test whether pre- and post-cardioversion treatment with the ARB candesartan (Atacand) would increase the length of time spent in sinus rhythm after electrical cardioversion. The researchers speculated that inflammation might play a role in determining the efficacy of cardioversion and that candesartan therapy might therefore be beneficial since there is some indication that it may help to reduce inflammation in the cardiac wall.
The clinical trial involved 171 patients with persistent AF who were randomized to receive a placebo or candesartan (8 mg/day pre-procedure and 16 mg/day post-procedure) for 3-6 weeks prior to cardioversion and for 6 months following cardioversion. Serum levels of inflammatory markers – high-sensitivity C-reactive protein (hs-CRP), tumor-necrosis factor alpha, interleukin-6, P-selectin, E-selectin, CD-40 ligand, and vascular cell adhesion molecule-1 – were measured at baseline and end of study.

After 6 months 40 patients (26%) were still in sinus rhythm, while the remaining 74% had not been successfully cardioverted or had experienced one or more afib episodes since their initially successful conversion (usually within 2 weeks after cardioversion). The researchers observed that the patients still in sinus rhythm after 6 months had significantly lower levels of hs-CRP and E-selectin than did those who relapsed into AF. As a matter of fact, patients with an hs-CRP level above 5.22 mg/L (0.52 mg/dL) had a 60% increased risk of relapse compared to patients with lower levels. There was no indication that candesartan therapy had any effect on inflammation markers, effectiveness of cardioversion, or afib recurrence. It is also of interest that successful restoration of sinus rhythm did not change the level of inflammatory markers.


Editor’s comment: This study confirms that a moderate to high level of systemic inflammation (elevated hs-CRP level) is detrimental to the maintenance of sinus rhythm after an initially successful electrical cardioversion. Thus, it may be beneficial for persistent afibbers awaiting cardioversion to take steps to bring their hs-CRP level down during the obligatory wait time prior to cardioversion. Inflammation and hs-CRP levels can be safely and effectively reduced by supplementation with such natural anti-inflammatory agents as fish oils, beta-sitosterol, Moducare, curcumin, boswellia, or Zyflamend.

Magnesium infusions in AF control

TORONTO, CANADA. Magnesium is effective in prolonging the atrial and atrioventricular nodal refractory periods. As afib cannot be initiated during refractory periods, this is clearly a good thing and may explain why many afibbers have experienced substantial benefit from magnesium supplementation. Unfortunately, several studies have shown that 50% or more of patients with atrial fibrillation suffer from hypomagnesemia – that is, a lower than normal blood serum magnesium concentration (less than about 0.8 mmol/L). Serum magnesium concentration is a fairly poor indicator of magnesium status since only about 2% of the body’s total magnesium stores are found in the blood. It is thus likely that substantially more than 50% of afibbers are magnesium deficient if intracellular levels are measured.

Researchers at the University of Toronto have just released the results of a meta-analysis of 8 clinical trials involving patients presenting with rapid atrial fibrillation. The trials compared the effect of magnesium infusions with placebo controls and patients given intravenous diltiazem or amiodarone. In the trials 1,200 to 10,000 mg of magnesium (as magnesium sulfate) was infused over a period of 1 to 30 minutes. In four of the studies magnesium infusion was continued for an additional 2 to 6 hours. Adequate rate control (ventricular rate below 100 bpm) was achieved in 61% of patients with magnesium as compared to 35% among controls. Magnesium was found to be as effective as diltiazem and amiodarone in achieving adequate rate control during the first hour. Magnesium was also found to be twice as effective as diltiazem or placebo in restoring sinus rhythm. Overall, the average time to conversion to sinus rhythm was 4 hours for magnesium as compared to 15 hours for placebo. The researchers conclude that magnesium infusions are safe and effective in achieving both rate and rhythm control in patients presenting with rapid atrial fibrillation.


Editor’s comment: It is hoped that emergency departments will take note of these findings and begin to treat acute cases of afib with magnesium infusions rather than with ineffective infusions of digoxin, verapamil, or diltiazem. It would be
tempting to speculate that oral supplementation with magnesium might be effective in slowing heart rate and restoring sinus rhythm during an acute afib episode. However, I have not come across anything in the medical literature indicating that this would be so. Besides, achieving an intake of 1,200 mg of magnesium via oral ingestion would be pretty well impossible and likely to lead to massive diarrhea. Using magnesium infusions to help prevent afib episodes and ectopic beats would, however, make sense since it is very difficult to correct hypomagnesemia just by oral supplementation.

Differences between AF and atrial flutter

VANCOUVER, CANADA. Canadian researchers have compared stroke incidence and mortality between a group of 781 patients with newly-diagnosed AF and 96 patients with newly-diagnosed atrial flutter. Most of the patients had underlying heart disease or hypertension, but 19% were classified as having lone AF, while 17% were classified as having lone atrial flutter. The patients were followed for an average (median) of 6.9 years during which time 65 ischemic strokes (10 fatal) and 7 hemorrhagic strokes (5 fatal) occurred. This corresponds to an annual stroke rate of 1.33% a year among afibbers and 1.24% a year in patients with atrial flutter. Not a significant difference, but certainly well below the 5-fold increase in stroke risk often quoted for patients with AF.

It is of interest that 57% of afibbers and 43% of atrial flutter patients were on warfarin at the time of their stroke. The estimated overall mortality rate in the group was about 3% a year with no significant difference between afibbers and atrial flutter patients. There were no strokes in the lone atrial flutter group (no mention is made in the report of strokes in the lone AF group) and patients with lone atrial fibrillation or flutter were found to have significantly smaller left atria than those with hypertension or underlying heart disease.

The researchers also observed that 28% of patients originally presenting with atrial flutter later converted to AF. They question the hypothesis that the main cause of ischemic stroke in atrial fibrillation and flutter is the formation of clots in the left atrial appendage and point out that high-risk patients with AF have been found to have a 63% incidence of aortic plaque. Thus, ischemic strokes in atrial fibrillation and atrial flutter patients are more likely related to comorbid conditions than to the fibrillation or flutter as such.


Editor’s comment: The observation that atrial fibrillation and atrial flutter involve comparable risks of stroke and overall mortality is indeed interesting as is the observation that stroke risk may be more related to comorbid conditions than to fibrillation or flutter as such. This supports my own long-held conviction. It is also of interest that over half of the study participants were on warfarin when they suffered their stroke – not exactly a ringing testimony to the effectiveness of warfarin!

Long-term progression of lone AF

ROCHESTER, MINNESOTA. More than 50 years ago cardiologists at the Mayo Clinic began following a group of lone afibbers in order to determine their long-term prognosis and survival. The group consisted of 34 participants with the paroxysmal variety, 37 with persistent afib, and 5 with permanent afib at entry to the study. Lone AF was defined as atrial fibrillation without underlying structural heart disease or hypertension (no age limitation). Atrial fibrillation was defined as paroxysmal if it terminated on its own, as persistent if cardioversion (electrical or drug-assisted) was required to terminate episodes, and as permanent if sinus rhythm could not be restored or maintained despite intervention. The average age at diagnosis was 44 years and 78% of the group was male. Thirty-four percent of study participants were prescribed digoxin within 30 days of their first episode. The number of “digoxin users” had increased to 75% at the latest follow-up.

After an average follow-up of 30 years, 29% of paroxysmal and persistent afibbers had progressed to permanent AF. It is interesting to note that 68% of persistent afibbers became paroxysmal and 22% became permanent during follow-up. Only 6% of
paroxysmal afibbers became persistent, while 41% became permanent. In most cases the progression to permanent AF occurred within the first 15 years after diagnosis.

Survival in the study group at 92% at 15 years and 68% at 30 years was similar to or even slightly better than expected for an age- and sex-matched group of Minnesotans (86% and 57% at 15 and 30 years respectively). Twelve of the reported deaths were due to cardiovascular causes, while the remaining 15 deaths were due to other causes. The development of congestive heart failure (19% of group at 30 years follow-up) was not significantly higher than expected (15%).

During the follow-up, 5 strokes (0.2%/person-year) and 12 transient ischemic attacks (0.5%/person-year) occurred in the group – mostly among permanent afibbers. All strokes and TIAs occurred in participants who had developed one or more risk factors for stroke during follow-up (hypertension in 12 patients, heart failure in 4, and diabetes in 3). Not a single stroke or TIA occurred among lone afibbers with no risk factors for stroke. This prompted the following remark from the researchers:

*Our long-term data suggest that the increased risk of stroke in atrial fibrillation is due to “the company it keeps”.*

In other words, lone atrial fibrillation as such is not a risk factor for ischemic stroke. The overall conclusion of the study is highly reassuring to lone afibbers.

After >30 years of follow-up of our rigorously defined cohort, findings confirm that overall survival is not affected adversely by lone atrial fibrillation.

In an accompanying editorial, Dr. Lars Frost of the Aarhus University Hospital in Denmark makes the following interesting comment, *Cardiologists with strong political influence have suggested that a diagnosis of lone atrial fibrillation should be restricted to patients <60 years of age, although there is not evidence of any threshold values by age regarding the risk of stroke in patients with atrial fibrillation – or in any other medical condition for that matter.*


**Editor’s comment:** It is indeed encouraging to receive further confirmation that lone AF does not shorten lifespan nor increase stroke risk. It is also a cause for celebration that the conversion from paroxysmal and persistent AF to permanent is less than 1% per person-year. It is likely that it would have been closer to 0% if the majority of study participants had not been prescribed digoxin. This “medicine from hell”, for lone afibbers at least, may not only prolong episode duration, but may actually convert paroxysmal AF to permanent.[1,2]


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**Efficacy and safety of amiodarone questioned**

PITTSBURGH, PENNSYLVANIA. Amiodarone (Cordarone, Pacerone) is usually considered the most effective drug for the suppression of atrial fibrillation and maintenance of sinus rhythm. On the other hand, its serious adverse effects make its long-term use problematical. Researchers at the University of Pittsburgh have just released the results of a study aimed at determining the sustainability and safety of long-term amiodarone therapy.

The study involved 168 afib patients who were treated with amiodarone and followed for 3 years. Seventy-seven percent of the group had paroxysmal AF, while the remaining 23% had the persistent variety. Most of the participants had hypertension (53%), coronary artery disease (27%) or congestive heart failure (19%), and 47% had a pacemaker or ICD (implanted cardioverter-defibrillator) – in other words, a fairly sick group and not necessarily representative, in their response to amiodarone, of a group of lone afibbers. The follow-up included routine visits to the clinic every 6 months during which the patients’ symptoms and satisfaction with the therapy were discussed and extensive testing carried out including physical examination, ECG, liver and thyroid function tests, and a chest x-ray. Eye examinations were
The efficacy of the amiodarone treatment was not impressive with 51% of the group reporting one or more AF episodes following the first 3 months of therapy. Patient satisfaction with the treatment was also less than sterling with 55% discontinuing it because of ineffectiveness (25%), intolerance (12%), or toxicity (18%). Intolerance to the drug showed up as fatigue, insomnia, nausea, vomiting, constipation, tremor, weakness, blurred vision, nocturnal halo vision, and photosensitivity. The most serious adverse effect was pneumonitis (inflammation of the lungs), which occurred in at least 7% of the patients and most often signaled its presence with the development of an unexplained cough. Four percent of study participants developed hyper- or hypothyroidism, 3% developed liver toxicity (ALT and/or AST more than 3 times upper limit of normal), 2% developed vision problems, and 1% developed cardiac problems (bradycardia or ventricular tachycardia). The researchers conclude that for most patients a less than 50% chance for short-term success of an elective, potentially toxic therapy is not acceptable.

In an accompanying editorial, Dr. John Hill of the Princess Alexandra Hospital in Brisbane, Australia points out that amiodarone also increases the bleeding risk associated with warfarin therapy and that afibbers with a low body mass index (BMI) are more likely to develop pulmonary fibrosis from amiodarone therapy than are their more corpulent confreres.


Editor's comment: This study confirms the result of the survey reported in my first book Lone Atrial Fibrillation: Towards A Cure. Here 41% had found amiodarone therapy beneficial, while 59% reported serious side effects with the most common being thyrotoxicosis. Amiodarone is truly a drug of last resort for lone afibbers and is doubly dangerous without adequate and frequent follow-up examinations and tests.

**New scale for measuring AF severity**

TORONTO, CANADA. “Because of its high incidence and the considerable disability that it may generate, atrial fibrillation (AF) is increasingly recognized as an important clinical problem in medical practice” and “the primary purpose of any therapy in AF is to improve patient well-being”. These two statements do, in my opinion, signal a quantum shift in medical thinking about afib. Not only do they recognize that afib can generate considerable disability – ie. cannot be dismissed as a mere “nuisance”, but also that patient well-being, not stroke prevention, should be the attending physician’s primary concern, especially in regard to lone afibbers.

The above statements are contained in a report prepared by a group of Canadian EPs and cardiologists describing the development of a new scale for gauging the severity of afib. The scale is called the “Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale” or CCS-SAF Scale for short.

Afib is classified as first documented episode, recurrent paroxysmal, recurrent persistent, or permanent where paroxysmal episodes are defined as being self-terminating, persistent episodes as requiring medical intervention for termination, and permanent afib as not being convertible to normal sinus rhythm.

Rating an afibber on the Scale begins by determining the symptoms – palpitations, dyspnea (shortness of breath), dizziness, syncope (light-headedness or fainting), chest pain, weakness, or fatigue, accompanying documented AF. The severity of these symptoms is then assigned to one of five classes. Class 0 indicates that the afib is asymptomatic. Class 3 indicates a moderate effect on the patient’s quality-of-life such as moderate awareness of symptoms on most days in patients with persistent/permanent AF, or more common episodes (eg. more than every few months), or more severe symptoms, or both, in patients with paroxysmal afib. Class 5 indicates a severe effect on quality-of-life and would include frequent and highly symptomatic episodes in patients with paroxysmal afib or episodes accompanied by syncope.
The Scale is now in the process of being tested. Preliminary results indicate that it is valid and reliable in providing an estimate of the effect of AF on a patient’s quality-of-life.  


**Editor’s comment:** The development of the CCS-SAF Scale is a welcome development and a good start in giving AF, especially lone AF, the attention it deserves. It should also be a useful tool in deciding on priorities in regard to ablation and maze procedures. I am a bit surprised that the Scale does not address the question of afib burden (number of episodes times duration), but perhaps this very valid measure of afib severity will be added later.

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**Folic acid reduces risk of stroke**

BEIJING, CHINA. There is substantial evidence that high levels of the amino acid homocysteine increase the risk of atherosclerosis and ischemic stroke. Homocysteine levels can be reduced by supplementation with B vitamins, specifically folic acid, vitamin B6, and vitamin B12. It is, however, not clear whether B vitamin supplementation as such decreases the risk of stroke and cardiovascular disease. Now a group of Chinese researchers report that folic acid supplementation is indeed effective in reducing the risk of ischemic stroke.

The researchers analyzed data from 8 randomized clinical trials involving almost 17,000 participants. The trials compared folic acid supplementation (with or without combination with vitamins B6 and B12) with either a placebo, a lower does of folic acid, or usual care for a minimum duration of 6 months. The researchers conclude that folic acid supplementation reduces stroke risk by 18% overall. Longer term supplementation (more than 3 years) results in a greater (29%) reduction in stroke risk as a homocysteine reduction of 20% or more. The beneficial effect of folic acid supplementation was found to be greater in countries where folic acid fortification of grains is not mandatory indicating perhaps that once an adequate folate status has been achieved, no further benefit is obtained by additional supplementation. The researchers also observed no benefit of supplementation in study participants who had already suffered a previous stroke. They conclude that folic acid supplementation is effective in the prevention of a first stroke (primary prevention).


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**The warfarin conundrum**

BOSTON, MASSACHUSETTS. Anticoagulation with warfarin is currently recommended for afibbers with one or more risk factors for ischemic stroke (hypertension, heart failure, diabetes, prior stroke, prosthetic heart valve, and age above 75 years). Warfarin therapy, unfortunately, is associated with an increased risk of major hemorrhage (internal bleeding) generally estimated at about 2%/patient-year. Major hemorrhage is defined as internal bleeding that is fatal, requires hospitalization with blood transfusion, or involves a critical site such as the brain. Although the indications for warfarin therapy generally increase with age, there is some concern that the risk of major hemorrhage may increase even more with age. Researchers at the Boston University School of Medicine now report that the rate of warfarin-related serious internal bleeding is much higher among afibbers 80 years or older than previously thought.

Their study included 472 afibbers most of whom (91%) had one or more risk factors for stroke and 35% of whom had coronary artery disease. Thirty-two percent were 80 years of age or older and 40% overall were on aspirin. All afib patients were started on warfarin (INR 2.0 – 3.0) at discharge from hospital and followed for a year. Management of warfarin therapy was done at the Massachusetts General Hospital. Highlights from the study are as follows:

- Only 58% of total time on warfarin was spent within the recommended window of 2.0 – 3.0 INR.
• Patients with the highest risk of ischemic stroke also experienced most of the bleeding.

• 13% of patients aged 80 years or older experienced a major hemorrhage during the first year of therapy as compared to 4.75% in the group younger than 80 years. The first 90 days of therapy were associated with a 3-fold increased risk.

• By the end of the first year, 134 patients (28%) had been taken off warfarin either because they had regained sinus rhythm or because they had suffered serious bleeding. In the age group 80 years and above, 81% of warfarin discontinuations were due to safety concerns.

The researchers conclude that previously published rates of bleeding during warfarin therapy underestimate the incidence actually experienced in clinical practice, particularly in the age group 80 years and above.


**Editor’s comment:** As is common in trials and studies involving warfarin, there was no comparison group in this study. Thus, it is not clear whether the benefit (avoidance of ischemic stroke) of warfarin outweighs the risks (major hemorrhage including often fatal hemorrhagic stroke) especially in older afibbers. As Dr. George Wyse of the University of Calgary states in an accompanying editorial, “It would be extremely useful if one were able to estimate a net benefit comparing the risk of bleeding and the risk of thrombotic stroke.”

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**Gender differences in AF treatment**

GRONINGEN, THE NETHERLANDS. Neither the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial nor the Rate Control Versus Electrical Cardioversion (RACE) study found any significant difference in mortality relating to the treatment of persistent afibbers with rate control versus rhythm control + cardioversions. Now Dutch researchers have taken a closer look at the RACE study results to see if the above finding applies to both men and women.

The RACE study involved 192 female patients and 330 males with persistent AF, ie. episodes that could only be terminated with cardioversion. The average age of the males was 67 years versus 71 years for females. Female patients were more likely to experience palpitation (33% vs 24%) and fatigue (47% vs 35%) during an episode than were men. Females in the study were also more likely to have hypertension (63% vs 41%) and diabetes (17% vs 6%) than were male participants. Men, however, had a higher incidence of coronary artery disease (31% vs 21%) and were more likely to have experienced a heart attack (19% vs 8%).

Lone afibbers accounted for 26% of male participants and 12% of female. Most participants (73%) were on anticoagulation medications. They were followed for an average of 2.3 years during which 21% of female patients and 19% of males reached the primary endpoint of death from cardiovascular causes (7%), heart failure, stroke (6.7%), bleeding, severe adverse effects from antiarrhythmic drugs, or pacemaker implantation.

Detailed analysis of the data, however, clearly showed that women randomized to rhythm control + cardioversion fared significantly worse than women assigned to rate control. The primary endpoint occurred in 33% of women treated with rhythm control versus 11% among those treated with rate control. Women on rhythm control were 3 times more likely to die from cardiovascular causes, 6 times more likely to develop heart failure, and 5 times more likely to experience thromboembolic complications (stroke) than were women assigned to rate control with beta-blockers, calcium channel blockers, or digoxin. Women generally scored lower than men on Quality of Life evaluations, but there were no differences in QoL scores between women on rate control and those on rhythm control.

The researchers conclude that rate control may be the preferable approach to women with persistent
AF since it clearly has far fewer adverse effects and does not result in a poorer quality of life than does rhythm control plus cardioversion.  

Editor’s comment: Although these findings are unlikely to be directly applicable to women with persistent lone AF, they do suggest the possibility that optimum treatment may be different for male and female afibbers.

Asymptomatic AF after ablation

CLEVELAND, OHIO.  The medical literature is inconsistent when it comes to the question – “How frequent are asymptomatic AF episodes after a seemingly successful pulmonary vein ablation?” Some studies have found a high incidence of post-ablation asymptomatic episodes, while others have found low to moderate levels.

EPs at the Cleveland Clinic now report the results of a recent study designed to determine the incidence of post-PVAI (pulmonary vein antrum isolation) AF in a group of 86 afibbers 34% of whom had structural heart disease.  All the study participants had previously had a permanent pacemaker implanted to deal with symptomatic sick sinus syndrome often exacerbated by antiarrhythmic or rate-control medications.  The patients (71% men) had suffered from afib for an average of 6.9 years and were 57 years of age on average; 65% were paroxysmal and 35% persistent, and all had highly symptomatic episodes.

After undergoing a standard PVAI the patients were followed for 9 months with clinic visits at 1, 3, 6, and 9 months.  Following the ablation the mode switching of the pacemaker was set to occur at an atrial sensed rate above 170 bpm (indicative of AF).  All patients were also equipped with rhythm transmitters.  Antiarrhythmic medication (sotalol, propafenone, flecainide or dofetilide) was continued for 2 months post-ablation.  Procedural success was defined as no afib episodes beyond 2 months post-PVAI off antiarrhythmic medication.  Prior to the ablation, pacemaker interrogation showed an average of 34 mode switch episodes (MSEs) per month.  These MSEs correlated with afib symptoms 91% of the time and their average duration was about 20 hours.

Of the 86 patients, 23% had symptomatic episodes following the PVAI, while 32% experienced asymptomatic episodes as detected by MSEs.  The asymptomatic episodes were significantly less frequent than symptomatic episodes and much shorter in duration (0.6 minutes versus 134 minutes average).  The incidence of asymptomatic episodes declined markedly with time so that at the 3-month check-up only 3% experienced numerous and sustained asymptomatic episodes.

The researchers conclude that about 30% of patients undergoing PVAI for highly symptomatic afib will have asymptomatic episodes after the procedure.  However, most of these episodes are short (less than 60-second duration) and become infrequent within 3 months post-procedure.  Sustained, asymptomatic episodes are uncommon.  

Editor’s comment: The main concern about post-procedure asymptomatic episodes is stroke risk.  If asymptomatic episodes are frequent and long-lasting then the decision to discontinue warfarin may be more difficult to make than if asymptomatic episodes are infrequent and short.  The Cleveland study supports the common practice of discontinuing warfarin 3 months after a successful ablation.