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VIRTUAL LAF CONFERENCE

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SUBJECT: *European Guidelines for Management of AF*

The European Society of Cardiology (ESC) and the European Heart Rhythm Association (EHRA) have just released their very extensive (60 pages with 200 references) 2010 guidelines for the management of atrial fibrillation. Cardiologists and electrophysiologists from 14 European countries were involved in this very major project. It is estimated that over 6 million Europeans now suffer from atrial fibrillation (AF), the most common cardiac arrhythmia seen in clinical practice. Its "true" prevalence is estimated at 2% and this number is expected to double in the next 50 years. The lifetime risk of developing AF is about 25% in those who have reached the age of 40 years.

Most AF patients are symptomatic, but about one-third are not aware of their arrhythmia (asymptomatic or silent AF). In most patients AF progresses from short, rare paroxysmal episodes to longer and more frequent episodes, and then to persistent and permanent associated with further development of the disease underlying the arrhythmia. The majority of AF cases involve such comorbidities as hypertension, heart failure, valvular heart disease, cardiomyopathy, congenital heart defects, coronary heart disease, thyroid dysfunction, obesity, diabetes, sleep apnea, chronic kidney disease, and chronic obstructive pulmonary disease (COPD). Aging increases the risk of AF primarily because of the increased risk of developing cardiovascular and other disease late in life.

Following are highlights from the guidelines. Please note that the focus is on AF with underlying heart disease and other comorbidities. Thus observations and recommendation may or may not apply to "lone" or "idiopathic" atrial fibrillation (LAF).

Types and Severity of AF

First diagnosed – Every patient who presents with AF for the first time falls in this category irrespective of how long he or she has actually had AF.

Paroxysmal – Self-terminating in less than 7 days, most often in less than 48 hours.

Persistent – Lasts longer than 7 days or requires termination by cardioversion.

Long-standing persistent – Persistent AF having lasted longer than one year before a rhythm control strategy is attempted.

Permanent – Is said to exist when the permanent presence of the arrhythmia is accepted by patient and physician and no attempts are made to control rhythm.

The severity of AF is classified as follows:

• EHRA I – No symptoms
• EHRA II – Mild symptoms; normal daily activity not affected
• EHRA III – Severe symptoms; normal daily activity affected
• EHRA IV – Disabling symptoms; normal daily activity discontinued

The authors note that, “It is also appropriate to inform the patient with lone or idiopathic AF about the good prognosis, once cardiovascular disease has been excluded”.

Management of AF

Management of AF patients is aimed at reducing symptoms and preventing complications, especially ischemic stroke.

A. Stroke Prevention

The main risk factors for stroke are:
• Prior stroke or transient ischemic attack (TIA)
• Hypertension
• Diabetes
• Structural heart disease
• Left ventricular systolic dysfunction (low ejection fraction)
• Age

• Type of AF (paroxysmal, persistent, permanent) does not influence the risk score and the need for stroke protection.
• Patients below the age of 60 years with no evidence of cardiovascular disease (lone afibbers) have a very low risk of stroke estimated at 1.3% over 15 years (cumulative).
• Stroke risk starts to rise after age 65 years and as patients get older stroke prevention therapy with antiplatelet agents (aspirin) becomes much less effective while the effectiveness of oral anticoagulation does not change.
• Uncontrolled hypertension increases stroke risk; however, there is evidence that well-controlled blood pressure is associated with a low risk of stroke and thromboembolism.
• Kidney disease affects stroke risk with a glomerular filtration rate less than 45 mL/min being associated with a 50% increase in stroke risk.
• The CHADS2 stroke risk score is a convenient way of estimating stroke risk in AF patients. A score of 1 is assigned to hypertension, congestive heart failure, diabetes, vascular disease, age 65 to 74 years, and female sex, whereas age of 75 years or older and having suffered a previous stroke or TIA warrants a 2 score.
• The evidence that aspirin protects against ischemic stroke is sparse indeed and for lone afibbers the daily ritual of an aspirin may actually be detrimental. In the Japan Atrial Fibrillation Stroke Trial, patients with lone AF were randomized to an aspirin group (aspirin at 150 – 200 mg/day) or a control group without antiplatelet or anticoagulation therapy. The incidence of stroke, TIA and cardiovascular death was 3.1%/year in the aspirin group vs. 2.4% in the control group. The incidence of major bleeding also tended to be higher in the aspirin group (1.6%) than in the control group (0.4%).
• In low-risk patients with no stroke risk factors (essentially lone afibbers below the age of 65 years with a CHADS2 score of 0) no anti-thrombotic therapy is the preferred option. For AF patients with a score of 1 oral anticoagulation (warfarin) or aspirin (75 – 100 mg/daily) may be used with oral anticoagulation being preferred. Aspirin may be preferable in women below the age of 65 years with a CHADS2 score of 1 solely due to their gender. Recommendations for AF also apply to patients with atrial flutter.
• The HAS-BLED score evaluates the risk of bleeding associated with antithrombotic therapy. A score of 1 is assigned for hypertension, previous stroke, previous bleeding, variable INR, age 65 years or older, abnormal kidney function, abnormal liver function, alcohol abuse, and use of aspirin or NSAIDs. A total score of 3 or higher indicates the need for caution in the initiation and follow-up of antithrombotic therapy.
• The recommended INR range for adequate stroke protection is 2.0 – 3.0. Many “real life” studies reveal that patients on warfarin are within this range less than 50% of the time, thus vastly overestimating the benefits of warfarin observed in tightly-controlled clinical trials.
• Self-monitoring of INR may be considered for patients who are physically and cognitively capable of performing the test.
• Cardioversion is associated with an increased risk of stroke. If an episode has lasted longer than 48 hours, 3 weeks of anticoagulation is required prior to cardioversion followed by 4 weeks after cardioversion. The 3-week pre-cardioversion period may be omitted or shortened if a TEE (transesophageal echocardiogram) shows no evidence of

thrombi (clots) in the left atrium or left atrial appendage.

B. Acute Rhythm and Rate Control

Although most paroxysmal afibbers convert to normal sinus rhythm (NSR) on their own within 24 – 48 hours, it is sometimes necessary to visit the emergency department to achieve NSR or at least bring the ventricular (pulse) rate down to a tolerable 80 to 100 bpm. Conversion to NSR can be achieved in two ways – pharmacological conversion and electrical cardioversion.

Pharmacological conversion
This is achieved by injection of an antiarrhythmic drug. Flecainide and propafenone are the most effective, but are not recommended for patients with underlying heart disease and abnormal left ventricular function. Ibutilide (Corvert) is effective for both atrial flutter and AF with conversion rates of 50% within 90 minutes. However, it can cause torsades de pointes and a significant increase in QT interval. Conversion with amiodarone occurs several hours later than with flecainide and propafenone with a conversion rate of 80 to 90% at 24 hours. Sotalol, verapamil, metoprolol and digoxin are not useful for pharmacological conversion, but metoprolol and verapamil are effective in slowing the heart rate.

It is also possible to use propafenone and flecainide orally to convert to NSR. In one trial AF terminated in 45% of patients given propafenone within 3 hours as compared to 18% among those given a placebo. Flecainide has a similar effect. Both propafenone (450 – 600 mg) and flecainide (200 – 300 mg) can be used on-demand (pill-in-the-pocket) approach by patients experiencing episodes monthly or less frequently. Both drugs should be taken as soon as possible after the onset of an episode.

Electrical cardioversion
A detailed discussion of electrical cardioversion can be found at http://www.afibbers.org/resources/cardioversion.pdf. The procedure is associated with a 1 to 2% risk of thromboembolism and ventricular tachycardia and fibrillation may occur in patients on digoxin or those deficient in potassium. Pre-treatment with amiodarone, ibutilide, flecainide, propafenone and sotalol increases the likelihood of successful cardioversion.

C. Long-term management

The long-term management of AF may involve rate control, rhythm control, or a combination of both. In rate control the patient is prescribed beta-blockers or calcium channel blockers (verapamil or diltiazem) with the goal of maintaining a ventricular rate below 100 bpm, but no attempt is made to convert the patient to NSR. In rhythm control the patient is treated with an antiarrhythmic drug (amiodarone, flecainide, propafenone, disopyramide, dronedarone or sotalol) with or without the use of rate control drugs.

The commonly held view is that there is no difference in stroke rate, overall mortality and quality of life between rate and rhythm control. This conclusion is mainly based on the results of the AFFIRM trial which, in my opinion, was seriously flawed and not applicable to lone afibbers. The AFFIRM trial involved 4060 patients with persistent AF and a mean age of 70 years. Seventy-one per cent had a history of hypertension, 38% had coronary artery disease, and 26% had impaired left ventricular function. Only 12% had lone AF. Half the patients were randomized to rate control plus anticoagulation, while the other half was randomized to rhythm control plus anticoagulation. After 5 years of follow-up 21.3% of the patients in the rate control group had died as compared to 23.8% in the rhythm control group.

So how do these findings affect lone afibbers, particularly paroxysmal ones? To quote the authors of the study, “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 has 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 do, in my opinion, significantly detract from the value of the AFFIRM study, particularly in the case of lone afibbers.

The authors of the new European guidelines seem to agree that rhythm control is preferable to rate control when it comes to quality of life. They state, “quality of life is significantly impaired in patients with AF compared with healthy controls, and post-hoc analyses suggest that maintenance of sinus rhythm may improve quality of life and be associated with improved survival.”

Other observations
• Amiodarone should only be used in patients who have failed treatment with other antiarrhythmic drugs or have significant structural heart disease. It should not be used in patients with permanent AF.

• In patients with no or minimal heart disease, beta-blockers represent a logical first attempt to prevent recurrent AF when the arrhythmia is clearly related to mental or physical stress (adrenergic AF). Since beta-blockers are not very effective in many other patients with lone AF, flecainide, propafenone, sotalol, or dronedarone is usually prescribed. Disopyramide, which has marked anticholinergic effects, may be useful in vagally mediated AF.

• Patients with coronary artery disease should not receive flecainide or propafenone. Dronedarone or sotalol should be administered as first-line therapy with amiodarone being the drug of last resort. Sotalol prolongs QT interval, may induce torsades de pointes and should not be used in patients with heart failure or left ventricular hypertrophy.

Left Atrial Catheter Ablation

Catheter ablation is now an accepted alternative to therapy with antiarrhythmics and rate control drugs, but should be reserved for patients who remain symptomatic despite optimal medical therapy. The authors of the guidelines make the following observations:

• Operator experience is an important consideration when contemplating ablation as a treatment option.

• Since amiodarone treatment may be associated with serious and frequent adverse effects, especially during long-term treatment, it is reasonable to consider catheter ablation as an alternative to amiodarone treatment in younger patients.

• Patients with heart failure benefit from ablation as it results in improved ejection fraction and exercise tolerance.

• Ablation of complex fractionated atrial electrograms on its own (without isolation of the pulmonary veins) is not effective in eliminating paroxysmal AF.

• Catheter ablation for AF should include a right atrial flutter ablation if there is any evidence of flutter prior to or during the primary ablation procedure.

• A recent meta-analysis found a 77% average success rate for catheter ablation vs. 52% for medical therapy.

Prevention of AF

Upstream therapy to prevent or delay myocardial remodeling associated with inflammation, hypertension and heart failure may help prevent the development of AF or, once established, may reduce its rate of recurrence or progression to permanent AF.

• Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) may help prevent inflammation and resulting fibrosis, and have been found effective in patients with hypertension and congestive heart failure.

• Patients with primary hyperaldosteronism have a 12-fold increased risk of developing AF. Several trials to evaluate the effects of spironolactone and eplerenone in this patient group and in afibbers with hypertension are underway.

• There is no compelling evidence that statin drugs are effective in preventing the development or recurrence of AF except in the case of AF associated with bypass surgery.

• There is no robust evidence to make any recommendation regarding the possible benefits of fish oil (eicosapentaenoic acid and docosahexaenoic acid) in preventing the establishment and recurrence of AF.

• There is increasing evidence that AF is 2 to 10 times more prevalent in active or former competitive athletes and those performing intense recreational endurance sports.

• Atrial fibrillation is often associated with hyperthyroidism and may disappear if normal thyroid function is attained.

Conclusion

Although the new European guidelines for the management of atrial fibrillation are primarily aimed at afibbers with underlying heart disease, they do contain points of specific interest to lone afibbers.

• Patients below the age of 60 years with no evidence of cardiovascular disease (lone afibbers) have a very low risk of stroke estimated at 1.3% over 15 years (cumulative).

• Uncontrolled hypertension increases stroke risk; however, there is evidence that well-controlled blood pressure is associated with a low risk of stroke and thromboembolism.

• The evidence that aspirin protects against ischemic stroke is sparse indeed and for lone afibbers the daily ritual of an aspirin may actually be detrimental. In the Japan Atrial Fibrillation Stroke Trial, patients with lone AF were randomized to an aspirin group (aspirin at 150 – 200 mg/day) or a control group without antiplatelet or anticoagulation therapy. The incidence of stroke, TIA and cardiovascular death was 3.1%/year in the aspirin group vs. 2.4% in the control group. The incidence of major bleeding also tended to be higher in the aspirin group (1.6%) than in the control group (0.4%).

• In low-risk patients with no stroke risk factors (essentially lone afibbers below the age of 65 years with a CHADS2 score of 0) no anti-thrombotic therapy is the preferred option.

• For AF patients with a score of 1 oral anticoagulation (warfarin) or aspirin (75 – 100 mg/daily) may be used with oral anticoagulation being preferred. Aspirin may be preferable in women below the age of 65 years with a CHADS2 score of 1 solely due to their gender. Recommendations for AF also apply to patients with atrial flutter.

• In patients with no or minimal heart disease, beta-blockers represent a logical first attempt to prevent recurrent AF when the arrhythmia is clearly related to mental or physical stress (adrenergic AF). Since beta-blockers are not very effective in many other patients with lone AF, flecainide, propafenone, sotalol, or dronedarone is usually prescribed. Disopyramide, which has marked anticholinergic effects, may be useful in vagally mediated AF.

ESC/EHRA. Guidelines for the management of atrial fibrillation. **European Heart Journal**, *Vol. 31, 2010, pp. 2369-2429*

Hans

Thanks for the summary Hans. Prystowsky gave a talk at the recent ESC congress about the new guidelines and indicated that it is an update from the 2007 HRS consensus guidelines. I haven't done a comparison to see what is updated. If you have done a comparison, I would greatly appreciate your comments with regard to what's new or more definitive. Thanks.

Researcher

Thank you.

As I progress toward persistent AF, I have been considering an anticoagulation drug. After 7+ years my episodes are now bi-weekly, lasting 24-72 hours on average. As I am a 43 year old male, with a CHAD of 0, I see that no anticoagulation is the preferred option. I have also settled to very mild, almost asymptomatic afib events, so no rate control is necessary. Attempts at pharmaceutical rhythm control have failed.

Am I understanding this report correctly-I should do nothing? (I will continue an organic diet, avoiding MSG)

I don't see any mention in the report about electrolyte deficiencies, gluten or dairy sensitivity. Are these not considered important contributing factors? I know there are many other studies where these factors are considered. Does European mainstream medicine not consider these important? If not, why? And, does this conflict with the information gathered in other studies?

Curt R

Researcher,

I have not studied the 2007 HRS consensus guidelines so I can't say what is different.

Hans

Curt,

The following statement from the guidelines would appear to apply to your situation:

"In low-risk patients with no stroke risk factors (essentially lone afibbers below the age of 65 years with a CHADS2 score of 0) no anti-thrombotic therapy is the preferred option."

I am afraid neither North American nor European mainstream medicine considers gluten or dairy sensitivity important factors in atrial fibrillation prevention.

Hans

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