

Electrical Cardioversion for Atrial Fibrillation. Are There Indications Left After the AFFIRM Study?

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Atrial fibrillation is the most common arrhythmia found in clinical practice. It doubles the mortality rate in affected patients and the condition is associated with a greater risk of stroke. Over the past decade, arrhythmia specialists have concentrated on determining the etiology and physiopathology of this disease. Such efforts have provided a fresh view on the onset, perpetuation and treatment of this arrhythmia. Until present, though, most patients have received traditional treatment, that is, antiarrhythmic drugs and/or electrical cardioversion. Electrical cardioversion of persistent atrial fibrillation is a very effective treatment for restoring sinus rhythm, though recurrence is common. Many recurrences are a clinical consequence of electrical remodeling in atrial tissue, with a shortening of the refractory period.

One of the clinical problems we face when dealing with atrial fibrillation is to establish a classification that has prognostic and therapeutic implications. The new clinical classification of atrial fibrillation asserts that the condition can be paroxysmal (generally self-limiting, with episodes lasting less than seven days), persistent (not self-limiting, lasting for more than seven days) or permanent, in which no cardioversion is performed or the heart rate is maintained and the patient continues with chronic atrial fibrillation. We know that when atrial fibrillation episode persists for more than a year, the chances of subsequently maintaining sinus rhythm decrease steadily.

The therapeutic options for treatment of atrial fibrillation have been the object of clinical study published recently in the *New England Journal of Medicine*: The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.¹ The AFFIRM study tried to determine whether electrical cardioversion and antiarrhythmic drugs to

maintain sinus rhythm were better than drugs to slow atrioventricular node conduction, controlling ventricular response. The randomized multicenter study compared the two therapeutic strategies in patients with atrial fibrillation and a high risk of stroke or death.

The primary outcome measure was overall mortality. The study included 4060 patients, 70.8% with a history of hypertension and 38.2% with coronary disease. There were 356 deaths in the group of patients assigned to control of heart rhythm, while in the group with heart rate control, there were 310 deaths (the mortality at five years was 23.8 and 21.3%, respectively; $P=.08$). More patients assigned to the group for control of heart rhythm required hospitalization compared to the group with heart rate control. There were also more adverse drug effects reported in the rhythm control group. In both groups, most episodes of stroke occurred after subjects had stopped taking warfarin or when their international normalized ratio fell in the subtherapeutic range. The results from the AFFIRM study showed that management of atrial fibrillation based on control of heart rhythm did not offer any survival advantage compared to a strategy based on heart rate control.

These results are not surprising and are in agreement with previous studies that have investigated this topic. In the PIAF study,² 252 patients with persistent atrial fibrillation (lasting for at least seven days but not more than a year) were randomized to strategies of electrical cardioversion (with anticoagulants and amiodarone) or ventricular rate control (with anticoagulants and 90 or 180 mg of diltiazem twice a day). Only 10% of patients with heart rate control had sinus rhythm after one year, compared to 50% of patients in the group treated with cardioversion, though patients in this group were hospitalized more often because of repeated cardioversion treatment. After a year, the symptoms were similar, but exercise tolerance was worse in the group with heart rate control.

The RACE study³ (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation), published at the same time as the AFFIRM study, also

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compared strategies for control of heart rate with those that control rhythm (in this case by electrical cardioversion) in patients with persistent atrial fibrillation. The primary outcome measure was defined as a composite of death from cardiovascular causes, hospitalization for heart failure, thromboembolic complications, serious bleeding, implantation of a pacemaker and severe adverse events related with treatment. The incidence of these combined events was 17.2% in the group with heart rate control and 22.6% in the group with rhythm control ($P=NS$). Thus, the strategy of control of ventricular response does not have a higher morbidity/mortality than the strategy of heart rhythm control in patients at high risk of recurrence of atrial fibrillation.

How then should the results of these studies change our approach to the management of patients with atrial fibrillation? Before reaching a decision, we should consider multiple clinical factors and also be aware of the limitations of the AFFIRM study. First, we should remember that if we choose to maintain sinus rhythm in patients with a high risk of recurrence of arrhythmia, they will probably require more aggressive chronic anticoagulation therapy than that indicated in current consensus guidelines for treatment of atrial fibrillation. In the AFFIRM study, 72% of strokes occurred in patients who were receiving no or suboptimal anticoagulation therapy. We should not forget that most patients in this study experienced more than one episode of atrial fibrillation. As we mentioned earlier, these patients have a higher probability of recurrence due to atrial remodeling. Thus the conclusions of the AFFIRM study cannot be extended to patients suffering their first episode of atrial fibrillation, whatever their age. We should also mention other limiting aspects of the study design, namely, some centers may not have included highly symptomatic patients to prevent them from being assigned to heart rate control. The results, then, cannot be applied to patients with highly symptomatic paroxysmal recurrent atrial fibrillation. Furthermore, the study did not include young patients with no risk factors for stroke, so the results do not apply to this population group.

Surprisingly, it is barely mentioned that a large proportion of patients assigned to the group with heart rate control had sinus rhythm at the end of follow-up (34.6% at the visit after five years versus 62.6% after five years in the group with heart rhythm control). Therefore the clinical characteristics of this cohort cannot exactly represent the prognosis in patients with chronic atrial fibrillation managed by ventricular control. Likewise, we should not forget that there is an important difference in the use of beta-blockers. These drugs were used less in the group with heart rhythm control at the start of the study (21.8% vs 46.8% in the

group with heart rate control) and throughout the study (49.6% in the group with heart rhythm control and 68.1% in the group with heart rate control).

Conversely, the possible advantage of maintaining sinus rhythm in patients may be masked by the adverse effects of the antiarrhythmic drugs used in these studies (the AFFIRM study protocol permitted the use of amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine sotalol and combinations of these drugs). More than a decade ago, Coplen et al published the results of a meta-analysis with quinidine. This drug was clearly effective at preventing recurrences of atrial fibrillation, but it increased the mortality rate (odds ratio 2.98; $P<.05$). After the CAST study,⁴ not many antiarrhythmic drugs have shown a neutral effect on survival, even in conditions that induce electrical instability, such as myocardial infarction. Amiodarone, however, is one of the exceptions as the EMIAT⁵ and CAMIAT⁶ studies have shown. The CTAF study also included amiodarone, and found the drug to be more effective than propafenone and sotalol for preventing recurrences of atrial fibrillation. Both the AFFIRM and RACE studies were probably designed before the results from the CTAF study were published in 2000.⁷

Recently, the therapeutic options for treating atrial fibrillation have been extended by the introduction of new cardioprotective agents which are able to prevent remodeling or ion channel modification.⁸ Intracellular calcium may play an important part in electrical remodeling, though treatment with calcium antagonists has not always been effective.⁹ Different studies with angiotensin II receptor antagonists (ARA-II) and/or angiotensin converting enzyme (ACE) inhibitors have had a positive effect in the prevention of episodes of atrial fibrillation, both in humans and animals. Pedersen et al investigated the effect of trandolapril on the incidence of atrial fibrillation in patients with left ventricular dysfunction and found that the drug reduced the risk of developing atrial fibrillation by 55%. The ACE inhibitors could also have a beneficial effect through their action on fibrosis and apoptosis in the cardiovascular apparatus. A study performed by Nakashima et al showed for the first time that angiotensin II contributes to electric remodeling. In this study, candesartan or captopril were able to prevent shortening of the atrial effective refractory period during rapid atrial pacing, while angiotensin II had the opposite effect. More recent studies have shown that losartan is able to reverse fibrosis in hypertensive subjects, irrespective of the antihypertensive effect of the drug. Blockade of the angiotensin II type I receptor may therefore be associated with inhibition of the synthesis of type I collagen and a regression of myocardial fibrosis. Other studies have evaluated the effect of antiarrhythmic drugs on the potassium channels in atrial and

ventricular myocytes.¹⁰ Data collated from different studies with ACE inhibitors also confirm that the renin-angiotensin-aldosterone system acts as a mediator of atrial remodeling in atrial fibrillation.

Despite these pharmacological options, we should not forget that catheter ablation has been effective in the treatment of various types of arrhythmia. Some cases of atrial fibrillation could be treated by ablation of substrates responsible for supraventricular tachycardia and of arrhythmogenic foci in the pulmonary veins. We believe that the treatment strategies proposed in response to the results from the AFFIRM and RACE studies are not the best ones. Certainly new controlled and randomized studies are needed, probably with a combination of two drugs such as antiarrhythmic and non-antiarrhythmic agents, to provide a definitive answer to these questions. Patients with atrial fibrillation should also be pretreated before submitting them to electrical cardioversion. Such pretreatment is improving continually.

The immediate reaction to the AFFIRM study is that we should forget cardioversion of atrial fibrillation, but we think that such a response is clearly wrong. Instead, new recommendations should be established such as: *a*) control of heart rhythm may be acceptable depending on the clinical circumstances, age, and risk of stroke; *b*) many patients with persistent atrial fibrillation will continue to need chronic anticoagulation treatment regardless of the therapeutic option; *c*) in highly symptomatic patients such as those with diastolic dysfunction or intermittent recurrences of atrial fibrillation, control of heart rate may clearly be insufficient and sinus rhythm should also be controlled; *d*) in some older patients, and particularly in those with risk factors for stroke, cardioversion does not offer advantages and the results from the AFFIRM study should therefore be applied, and *e*) percutaneous ablation to treat atrial fibrillation is promising, as recognized in an editorial and article published recently in the REVISTA ESPAÑOLA DE CARDIOLOGÍA.¹¹ Ablation may be the therapeutic option of choice in certain patients with symptomatic paroxysmal atrial fibrillation that recurs despite medical treatment.

CONCLUSIONS

Older patients with persistent asymptomatic atrial fibrillation and risk factors for embolism are candidates for control of ventricular rate and chronic administration of anticoagulants. Electrical cardioversion is still clearly justified in many patients. Patients with episodes of recurring and refractory paroxysmal atrial fibrillation are ideal candidates for catheter ablation.

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