Therapeutic Success of a Prospective Cardioversion Protocol for Persistent Atrial Fibrillation

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INTRODUCTION

Atrial fibrillation (AF) is much more common than other types of arrhythmia. Its presence is associated with increased morbidity1 and mortality.2 Given that its prevalence increases with age,3,4 the number of patients with AF will continue to rise as the population...

Key words: Atrial fibrillation. Cardioversion. Antiarrhythmics. Recurrence.

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ages. Despite these epidemiological trends, the best therapeutic approach has yet to be defined.\(^1\) In recent years, a number of studies have been published that compare the strategy of restoring sinus rhythm with that of simple control of heart rate,\(^3,7\) though the findings of these studies have been controversial. In Spain, up-to-date information is lacking on the outcomes of electrical cardioversion (ECV) in unselected patients treated according to a strict protocol involving pretreatment, ECV, and follow-up. Information is also lacking on whether repetition of ECV after recurrence improves the long-term outcome and on whether continued administration of antiarrhythmics is beneficial after return to sinus rhythm. To address these questions, a study of ECV was undertaken and the results for the primary objective-determination of the therapeutic performance of isolated ECV as part of a strict protocol of pretreatment, ECV, and follow-up—are described here.

### METHODS

We prospectively included all consecutive patients with persistent AF lasting at least 1 month who were referred to the arrhythmia clinic of our center, a tertiary hospital with a centralized cardiology service catering for approximately 250,000 inhabitants. Patients were given the option of participating in an institutionally approved protocol of ECV together with standard antiarrhythmic treatment and clinical follow-up. Patients signed the informed consent before undergoing the intervention.

The inclusion criteria were presence of persistent AF lasting at least 1 month, age greater than or equal to 18 years, life expectancy greater than or equal to 1 year, and agreement by the patient to follow the protocol.

The exclusion criteria were presence of paroxysmal AF (defined as spontaneous return to sinus rhythm before starting antiarrhythmic treatment), contraindication for oral anticoagulants, and life expectancy less than or equal to 1 year.

Between October 2001 and November 2003, 364 patients with AF initially diagnosed as persistent were referred to our clinic, although 295 patients were finally included in the study. The main reasons for exclusion were refusal to follow the protocol (22 patients, 6%) and documented paroxysmal AF that was initially diagnosed as persistent (47 patients, 12.9%).

The protocol comprised 4 parts: a) clinical examination, b) pretreatment, c) ECV, and d) outpatient follow-up.

1. Clinical examination. A medical history was recorded, and the patients underwent a physical examination, general laboratory tests, and an echocardiographic study. The aim was to collect epidemiological data and information on personal history and onset of persistent AF, to rule out causes of secondary AF, and to investigate the presence of structural heart disease.

2. Pretreatment. This phase began with appropriate administration of oral anticoagulants, with monitoring of the international normalized ratio (INR) at least twice in 4 weeks. Outpatient antiarrhythmic treatment was then initiated. The first choice treatment was amiodarone at a loading dose of 600 mg/day for 1 week, followed by 400 mg/day for 1 week, and finally a maintenance dose of 1000 mg/week. In the event of contraindication or prior adverse reactions, either sotalol (target dose, 80 mg/8 h) or flecainide (target dose, 100 mg/12 h) was administered according to the characteristics of the patients. Patients who were unable to take any of these drugs started the protocol without the antiarrhythmic agent. The heart rate was controlled with beta-blockers or calcium channel blockers (verapamil or diltiazem). We made an effort to discontinue digoxin before ECV.

3. Electrical cardioversion. Before proceeding with ECV, appropriate oral anticoagulation therapy lasting at least 4 weeks had to have been administered or transesophageal echocardiographic findings had to rule out the presence of atrial or ventricular thrombi. Then after antiarrhythmic treatment lasting at least 3 weeks, ECV was performed in an outpatient setting with a monophasic defibrillator (Lifepack 9) using disposable self-adhesive pads in the modified anteroposterior position (right parasternal and left subscapular regions). A protocol of increasing DC shock energy was used, with up to 5 shocks being administered (200 J, 300 J, 360 J, 360 J with change of polarity, and 360 J with chest compression). Electrical cardioversion was considered effective when sinus rhythm was restored and maintained for at least 15 minutes of monitoring. If monophasic ECV was ineffective at restoring sinus rhythm, the patient was offered the possibility of internal ECV. If a bifasic defibrillator was available, bifasic ECV was offered. If sinus rhythm was restored during the pretreatment period after starting the antiarrhythmic agent, a pharmacologic cardioversion was recorded.

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**ABBREVIATIONS**

CVA: cerebrovascular accident.
ECV: electrical cardioversion.
AF: atrial fibrillation.
Outpatient Follow-up. During the first year after ECV, the period covered in this study, patients underwent clinical and electrocardiographic follow-up after the first month, then 3, 6, and 12 months after ECV or if new symptoms appeared. Follow-up started on the day the patient underwent ECV. When ECV was not effective because sinus rhythm could not be restored, the onset of AF was recorded as Day 0 and these events were excluded from the analysis of recurrences. Cases of lack of effectiveness of ECV due to early recurrences were, however, included in the analysis and counted as AF recurrence with onset at Day 0. Oral anticoagulation therapy was maintained for at least 1 month after ECV, with the possibility of discontinuing this medication if sinus rhythm was maintained during follow-up in accordance with clinical guidelines. Initial antiarrhythmic treatment was maintained during the first year after ECV. If a patient had to discontinue the first-choice antiarrhythmic therapy due to adverse reactions, a second-choice therapy was started. During follow-up, laboratory tests of thyroid, kidney, and liver function were done at 3, 6, and 12 months after ECV. A chest x-ray was taken at 6 months. In addition, clinical and electrocardiographic data and information on the treatments taken by the patient were collected during follow-up. We also recorded information on the recurrence of both persistent and paroxysmal AF, which were confirmed in all cases by a 12-lead electrocardiogram done at different scheduled visits or if a patient developed symptoms.

In the event of recurrence during the first year of follow-up, the patient was offered the possibility of undergoing a second and up to a third ECV, with follow-up starting again after each procedure. At the end of follow-up, the patients who had maintained sinus rhythm for at least 1 year and who tolerated the antiarrhythmic treatment were randomized to continue or discontinue treatment.

This article only reports the results of the first ECV and follow-up through to 1 year after ECV. The primary outcome measure was recurrence of persistent AF. Patients were censored on appearance of the first recurrence of persistent AF or when follow-up ended.

**Statistical Analysis**

The SPSS 10.0® program was used for analysis. Continuous variables were expressed as means±SD, and categorical ones as an absolute frequency and a percentage. Recurrence of persistent AF was considered as the endpoint for follow-up.

The Kaplan-Meier method was used for the survival analysis (time from ECV to recurrence of persistent AF). A univariate analysis was done by a log-rank comparison of the Kaplan-Meier curves to assess whether clinical variables (age, sex, hypertension, respiratory disease, presence of heart disease, type of heart disease, prior ECV, and duration of persistent AF) and echocardiographic variables were associated with recurrence of persistent AF. Only patients who achieved a sinus rhythm were included in this analysis. A Cox regression model (forward stepwise model) was used for the multivariate analysis. The model included variables with P-values less than .10 in the univariate analysis and those recognized in the past as relevant to the risk of recurrence. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Statistical significance was established at P<.05.

**RESULTS**

The baseline characteristics of the patients are presented in Table 1. The mean age of the study population was 68.7±10.7 years and 63.4% had a history of hypertension. The majority (62.7%) had some type of structural heart defect, although no left ventricular dilation or deterioration in ejection fraction was reported in most of the patients. In contrast, the left atrial diameter had increased in these patients (44.6±6.7 mm). This was the first episode of persistent AF in the large majority of patients-only 16.6% had undergone prior ECV procedures. Persistent AF lasted less than 1 year in 46.1% of the patients, was undocumented in 11.5%, and lasted more than 1 year in 42.4%. In 38.4% of the patients, AF had lasted less than 5 years. Amiodarone could be administered initially as the

| TABLE 1. Baseline Characteristics of the Study Population |
|----------|---------|
| Age, y (mean±SD) | 68.7±10.7 |
| Men | 62% |
| Hypertension | 63.4% |
| Structural heart disease | 62.7% |
| Hypertensive | 31.9% |
| Valvular | 24.1% |
| Ischemic | 17.6% |
| Dilated | 6.4% |
| Hypertrophic | 6.1% |
| Prior heart surgery | 7.8% |
| Respiratory disease | 11.9% |
| Prior electrical conduction procedures | 16.6% |
| Echocardiographic data |
| Ejection fraction, % (mean±SD) | 61.8±11.1 |
| LV diastolic diameter, mm (mean±SD) | 52±7.9 |
| Anteroposterior LA diameter, mm (mean±SD) | 44.6±6.7 |
| Ventricular septal thickness, mm (mean±SD) | 10.7±2.2 |
| Posterior LV wall thickness, mm (mean±SD) | 10.3±1.9 |

*LA indicates left atrial; LV, left ventricular.
Flecainide was used in 5.8% and sotalol in 5.4%, whereas only 1.4% of the patients did not take any antiarrhythmic agent.

Electrical Cardioversion

Sustained sinus rhythm was achieved in 93.2% (274 patients).

Pharmacologic cardioversion occurred in 9.5% (28 patients) after starting antiarrhythmic treatment. Monophasic ECV was performed according to the protocol described earlier in 267 patients, and was effective in 84.6%. Twenty-four patients required internal ECV or biphasic external ECV to restore sinus rhythm. Overall, sustained sinus rhythm was achieved with ECV in 92.5% (247 patients). Eleven patients (4.1%) did not achieve sustained sinus rhythm because ECV was ineffective and they refused to undergo internal or biphasic ECV. A further 9 patients (3.4%) experienced immediate recurrences.

Complications Associated With Electrical Cardioversion

Two patients had cerebrovascular accidents (CVA) after ECV despite appropriate anticoagulant therapy. One patient developed sinus dysfunction that required pacemaker implantation, 2 patients presented with discomfort in the skeletal muscles of the chest that required pharmacotherapy, and heart failure worsened in 5 patients in the first few days after ECV. All these patients had some type of structural heart disease with an ejection fraction greater than 50%.

Figure 1. Persistent AF free-survival curve for the whole population (A), by presence of prior electrical cardioversions (B), by left ventricular diameter (C), and AF duration (D). LVDD indicates left ventricular diastolic diameter; AF, atrial fibrillation.
Follow-Up

Median follow-up of the patients lasted 372 days, with an interquartile range (25%-75%) of 181-409 days. During the study, 4 patients (1.4%) were lost to follow-up and 9 patients (3.1%) died. Three of these deaths were of cardiovascular origin: 1 patient suffered ischemic CVA 3 days after ECV, 1 patient presented with worsening of heart failure 6 months after ECV, and 1 patient suffered ischemic CVA in the fifth month of follow-up. The other 6 deaths were due to noncardiovascular causes.

As reflected in the persistent AF recurrence-free survival curve after ECV (Figure 1A), 35.7% of the recurrences took place within 30 days of ECV if we include immediate recurrences. After 3, 6, and 12 months, the rates of recurrence were 46.5%, 50.4%, and 56.4%, respectively. If we exclude immediate recurrences during the first month, 33.5% of recurrences were reported in the first 3 months, 44.7% in the first 6 months, and 54.9% in the first year.

The univariate analysis of persistent AF recurrence-free survival during the first year after ECV is shown in Table 2. Figure 1B-D shows the Kaplan-Meier survival curves for each of the predictive factors.

In the multivariate analysis, the recurrence of persistent AF during follow-up was associated with duration of AF of more than 1 year, prior ECV procedures, and left ventricular diameter greater than 55 mm (Table 3), with adjustment for age, sex, heart disease, and left atrial diameter.

A score for risk of recurrence was calculated for each patient according to the presence of the different risk factors found in our population. One point was assigned for a history of prior ECV, ventricular diameter greater than 55 mm, and indeterminate duration of AF, and 2 points for AF lasting more than 1 year. Figure 2 shows the comparison of the cumulative probabilities of maintaining sinus rhythm during the first year after ECV according to the risk score. Recurrence-free survival in the first year is greater in the groups with a lower risk score.

During follow-up, 8.4% of the recurrences were in the form of paroxysmal AF (n=23), and the patients recovered sinus rhythm without the need to change the therapy or adjust the dose.

Change of Antiarrhythmic Drug

During the study, the antiarrhythmic treatment was changed in 32 patients (10.8%); 31 of these were taking amiodarone as the antiarrhythmic agent. Amiodarone had to be discontinued in 11.9% of the patients (n=31) who were taking the drug, primarily due to thyroid problems (Table 4).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
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<td>Prior electrical cardioversions</td>
<td>1.74</td>
<td>1.14-2.67</td>
<td>.01</td>
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<tr>
<td>LVDD &gt;55 mm</td>
<td>1.76</td>
<td>1.03-3.02</td>
<td>.04</td>
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<td>AF &gt;1 year</td>
<td>2.14</td>
<td>1.5-3.05</td>
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LVDD indicates left ventricular diastolic diameter; AF, atrial fibrillation.

DISCUSSION

Our study shows that a homogeneous protocol of preparation and ECV with prior antiarrhythmic therapy was able to restore sinus rhythm in a very high percentage of patients, and almost half of those still had sinus rhythm at 1 year after ECV. This was achieved with few complications. Only a prolonged history of AF, prior ECV procedures, and left
ventricular dilation were predictive of recurrence in our patients.

Treatment of AF is complex and still not fully defined. Prophylaxis against thromboembolism is the only aspect of treatment that is accepted without controversy, although a consensus for the exact duration of such therapy after restoring sinus rhythm has not been reached. For long-term treatment of these patients, 2 apparently opposing approaches can be taken, namely, control of heart rate or reestablishment of sinus rhythm. A number of clinical studies have recently focused on comparing the 2 approaches.6,7 No differences in long-term mortality were found in selected patient groups, but the strategy of rhythm control is more attractive in theory because the aim is to eliminate AF and, therefore, its consequences. In fact, different studies have shown that sustained sinus rhythm is an independent marker of survival,9,10 but this approach faces 2 main problems. First, it is hard to prevent recurrences of AF and, second, there is concern about the adverse reactions associated with many of the antiarrhythmic agents used. Atrial fibrillation has a strong tendency to recur, but the recurrence rates have varied greatly in different studies,11,12 due to the heterogeneous populations studied. The inclusion of persistent AF along with paroxysmal AF, AF associated with atrial flutter, the selection of patient subgroups not representative of patients seen in the clinic, and, finally, the wide variety of approaches used to recover and sustain sinus rhythm have made it difficult to extrapolate the findings of these studies to clinical practice. In our series, we have included consecutive patients referred for ECV in whom paroxysmal AF, secondary AF and intermittent AF had been ruled out. We excluded cases of atrial flutter, although prolonged history of AF was not an exclusion criterion. We applied a single approach in the preparation of patients for conversion to sinus rhythm and for preventing recurrences, a process which yielded a homogeneous study group representative of daily clinical practice in Spain.

Amiodarone has been shown to be highly effective at preventing recurrences in all populations studied15-17 and this drug has the advantage that it can be used by patients with structural heart disease or ventricular dysfunction without increasing mortality, unlike other antiarrhythmic agents.18 It was therefore the treatment of choice in our patients. Pharmacotherapy prior to ECV not only prepares the patient better for the procedure, but also achieves pharmacologic conversion of the arrhythmia in approximately 10% of the patients. This rate is lower than in other studies,17 probably because we included patients with a longer history of AF (at least 1 month) and excluded patients with paroxysmal AF. On the other hand, a wide range of adverse drug reactions have been attributed to this agent, reactions that affect, above all, the thyroid gland, skin, lung, and liver. In our series, the only clinically relevant effects were thyroid events, which

Figure 2. Persistent atrial fibrillation survival-free curve according to risk score.
required discontinuation of the drug in 23 cases (8.9%).

Given that the particular ECV technique used influences the immediate outcome of the intervention, we consider our findings, which were obtained with a standard protocol, to be more robust than those of other studies.47 Outcomes have been shown to be more favorable with anteroposterior positioning of the pads than with conventional positioning.48 We used a modified anteroposterior position that seems to be particularly favorable for ECV in patients with AF.29 Furthermore, we used self-adhesive pads, which contributed to ease of use. The effectiveness of ECV can be improved by using prior antiarrhythmic treatment,26 changing the polarity,27 using active chest compression,28 and applying biphasic shocks.24 The latter of these measures could not be applied systematically in our population because we did not have a biphasic defibrillator available at the start of the study. The sedation technique used also had a bearing on safety. Our patients were sedated with diazepam and low doses of etomidate, and no acute complications arising from the procedure were reported. With this approach, the technique could be applied in an outpatient setting; none of our patients required admission to hospital.

A higher incidence of recurrence was observed in our patients in the first 3 months, and particularly in the first month (33.5%), as has been reported in other series.11,14,24,26 The recurrence rate then stabilized, with an incidence of recurrences per year of 54.9% and an overall cumulative probability of recurrence in the population with normal sinus rhythm after 1 year of follow-up of 43.6%. In the different series reported in the literature, the findings vary according to the population studied and the use of antiarrhythmic agent, with recurrence rates ranging widely from 39% to 63% during the first month and from 36% to 83% at 1 year. Very high recurrence rates were reported in series of patients with persistent AF in whom prophylactic antiarrhythmic treatment was generally not used. After single ECV, Lundstrom et al11 reported a recurrence rate of 70% after 3 months and 77% after 1 year; Frick et al28 found a recurrence rate of 63% at 4 weeks after an effective ECV; in the study of Berry et al,44 the recurrence rate was 39% after 1 month and 62.5% after 1 year; Lefito et al27 in a cohort of 183 patients who received the first ECV, found a recurrence rate of 75% during the first year even though more than two-thirds were receiving antiarrhythmic treatment; and van Gelder et al11 in a series of 236 patients with no antiarrhythmic agents, reported that sinus rhythm was maintained 1 year after ECV in only 17% of the effective ECV procedures. In series in which most of the patients were taking antiarrhythmic agents, the recurrence rates are lower; in a series treated with amiodarone, Gosselink et al12 reported that 53% of the patients had sustained sinus rhythm 3 years after ECV; in the SAFE-T study,17 the group treated with amiodarone had a recurrence rate at 1 year of 48%; Ortiz et al30 retrospectively analyzed 118 patients, most of whom were being treated with amiodarone, and reported a recurrence rate of 35.6% after 1 year; and Bertaglia et al36 found a recurrence rate of 28% in the first week, 40% after 1 month, and 70% after 1 year, with all patients receiving class Ic or III antiarrhythmic agents. We should highlight that in most of these studies, the onset of persistent AF was recent (less than 3-7 days) and patients with persistent AF lasting more than 1 year were generally not included, and when such patients were included, they were in the minority. In contrast, in our series, all patients had been suffering AF for more than 1 year and 42% had persistent AF for at least 1 year; this longer history of AF will affect our findings but should also provide a better reflection of real clinical practice.

The independent predictors of recurrence were, as in other studies, prior history of ECV,12 longer duration of arrhythmia,11,14,26,27 and left ventricular dilation. This probably indicates that it is more difficult to sustain sinus rhythm in the particularly recurrent forms, recurrence associated with atrial remodeling due to prolonged presence of arrhythmia, and structural heart disease. Other indicators such as left atrial diameter,11,14 history of hypertension,11,14 and age11,14,26 were not predictive factors in our patients. We should highlight that the only predictive factor consistently reported in different studies is longer duration of atrial fibrillation.

The cumulative probability of sustaining sinus rhythm in the first year, according to our risk score, is 60.2% in patients with a score of 0, 48.3% in those with a score of 1, 32% in those with a score of 2, and 24.5% in those with a score of 3 or more. This score provides a simple way to stratify the risk of recurrence and may help to personalize the therapeutic approach for each patient, although this score should be validated in other populations to confirm its predictive value and thus its clinical usefulness.

It remains to be seen whether the therapeutic success can be improved with successive ECV done soon after recurrence without affecting safety. Likewise, the findings relating to another aim of the study, to assess the evolution after 1 year of follow-up, with and without maintaining antiarrhythmic therapy, will be known when all the patients have finished the second period of follow-up.

Limitations

Sinus rhythm could have been restored in more patients if a biphasic defibrillator had been available.
from the start of the study. In our series, 35.6% were taking renin-angiotensin system blockers. Such drugs in combination with amiodarone were shown, after starting the study, to facilitate the maintenance of sinus rhythm.\textsuperscript{33,34} If more patients had received this combination, we might have expected lower recurrence rates. The recurrence rates of paroxysmal AF were certainly underestimated because episodes are often asymptomatic.\textsuperscript{35}

**CONCLUSIONS**

After 1 year of follow-up, 43.6% of the unselected patients were still in sinus rhythm after a single ECV procedure when a homogeneous protocol of pretreatment with an antiarrhythmic agent, principally amiodarone, was followed. Few adverse reactions arising from the technique or antiarrhythmic treatment were reported after 1 year on dofetilide (DIAMOND) substudy. Such drugs were shown, after taking renin-angiotensin system blockers. Such drugs in combination with amiodarone were followed. Few adverse reactions arising from the technique or antiarrhythmic treatment were reported after 1 year of follow-up. Recurrence can be predicted with simple clinical variables, such as left ventricular dilation, duration of arrhythmia, and prior history of ECV.

**REFERENCES**