Aims To evaluate the impact, on atrial fibrillation (AF) recurrences, of verapamil addition to a class IC or III antiarrhythmic drug in patients, with persistent AF, who underwent an electrical cardioversion (EC).

Methods and results Three hundred sixty-three patients were randomized to receive four different pre-treatment protocols: oral amiodarone (group A), oral flecainide (group F), oral amiodarone plus oral verapamil (group A+V), oral flecainide plus oral verapamil (group F+V). Patients who showed an AF recurrence within 3 months were assigned to the alternative group and underwent a second EC after 48 h. During 3 months of follow-up, 89 patients (27.5%) had an AF recurrence. By univariate analysis, verapamil reduced AF recurrences if added to amiodarone or flecainide (from 35% to 20%, \( P = 0.004 \)). Applying Cox proportional hazards regression model, only the younger age, the shorter duration of AF, and the use of verapamil were predictor of maintenance of sinus rhythm after cardioversion. In patients with primary AF recurrence, verapamil addition to group A and F patients, significantly decreased secondary AF recurrence rate as compared to group A+V and F+V patients who stopped the verapamil therapy (68% vs 88%, \( P = 0.03 \)).

Conclusions The addition of verapamil to class IC or III antiarrhythmic drug significantly reduced the AF recurrences, that were more frequent in older patients and in patients with longer lasting AF; moreover, verapamil was effective in reducing the secondary AF recurrences, too.

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Introduction

Several studies, both in animals and in humans, have demonstrated that high atrial rates lead to atrial electrical remodelling, characterized by refractoriness and depolarization shortening and abnormal adaptation to rate. These electrophysiological changes facilitate atrial fibrillation (AF) recurrence and maintenance, after sinus rhythm restoration.1–3 Experimental animal studies have demonstrated that electrical remodelling can be prevented by verapamil administration,4,5 which reduces the number of immediate recurrences of AF after electrical cardioversion and extended the duration of sinus rhythm. Although further studies have not confirmed the benefit of verapamil on electrical remodelling6 several studies have investigated the role of calcium lowering therapy in patients with AF who underwent electrical cardioversion.7,8 Authors have investigated the role of calcium lowering therapy in patients with AF who underwent electrical cardioversion. However, also in the clinical setting, conflicting results have been reported.7–12 Aim of our multicentre, prospective, randomized study was to define if verapamil addition to a class IC or III antiarrhythmic drug based therapy reduces AF recurrences after electrical cardioversion.

Methods

Patient population

Three hundred and sixty-three out of 411 consecutive patients, referred to our centres for electrical cardioversion of persistent AF, were enrolled. Exclusion criteria were: (1) persistent AF lasting ≤21 days and >18 months; (2) previous history of sick sinus syndrome or pause >2.5 s during 24-h electrocardiographic Holter recording; (3) trifascicular block or any degree of atrioventricular block; (4) implantable pacing device; (5) previous history of sustained ventricular arrhythmia, cardiac arrest or congenital QT syndrome; (6) major hepatic or renal dysfunction; (7) history of myocardial infarction or a revascularization procedure within the previous 6 months; (8) signs of severe cardiac or respiratory insufficiency with a left ventricle ejection fraction <35%; (9) age <18 or >85 years; (10) left atrial thrombus.

Study protocol

All patients gave informed written consent to be enrolled in the study. Detailed clinical examination, thyroid function tests, electrocardiogram, chest radiography, transthoracic and transesophageal echocardiography were routinely performed. Verapamil, diltiazem, beta-adrenergic antagonists and all antiarrhythmic agents were stopped for at least five half-lives and for at least 1 month in the case of amiodarone before randomization. Oral anticoagulation, using warfarin sodium to obtain an INR of 2 to 3, started at least 3 weeks before electrical cardioversion. Patients enrolled were randomized to receive four different pharmacological treatment: oral amiodarone started 4 weeks before the cardioversion (group A); oral flecainide (200 mg/day) started 3 days before the cardioversion (group F); oral amiodarone started 4 weeks before cardioversion plus oral verapamil (240 mg/day) started 3 days before cardioversion (group A+V); oral flecainide (200 mg/day) plus oral verapamil (240 mg/day) started 3 days before cardioversion (group F+V). Amiodarone was given orally at 600 mg/day for 7 days, then at 400 mg/day for 7 days, and finally at 200 mg/day. All patients were followed up for 3 months. Patients who showed an AF recurrence within 3 months were assigned to the alternative group (A→A+V, F→F+V, A+V→A, F+V→F) and underwent a second cardioversion after 48 h. After each cardioversion cardiac rhythm was monitored by telemetry for at least 4 h and a 12-lead electrocardiogram was performed at 12, 24 and 36 h. Clinical examination and 12-lead electrocardiogram were scheduled, after hospital discharge, at 1 week, 30 and 90 days, and patients were instructed to obtain an electrocardiogram record in case of symptomatic palpitation.

Electrical cardioversion

During continuous 12-lead electrocardiographic monitoring and heavy sedation with propofol (2 mg/kg), up to three synchronized external monophasic shocks (200, 300, and 360 J) were delivered to restore sinus rhythm. Successful cardioversion was defined as restoring sinus rhythm for at least three beats. Patients in whom initial attempt of cardioversion was ineffective underwent internal cardioversion. In these patients two quadripolar catheters for pacing, sensing and defibrillation were located in the lateral right atrium and left pulmonary artery or coronary sinus. After sedation with diazepam (10 mg intravenously) or heavy sedation with propofol (2 mg/kg), during continuous electrocardiographic monitoring, biphasic shocks were delivered with a step-up protocol (5 →10 →30 J) until sinus rhythm was restored.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and were compared using a two-tailed Student’s t test for paired and unpaired data. A value of P < 0.05 was considered statistically significant. Fisher exact test was used to compare proportions. Atrial fibrillation-free survival data were analysed with the Cox proportional hazards regression model.

Results

Patients characteristics

Twenty-three patients (6.3%) enrolled (six patients in group A, seven in group F, six in group A+V, and four in group F+V, without any significant difference between patients taking or not verapamil) recovered the sinus rhythm spontaneously, before the cardioversion, whereas 10 out of 13 patients (four patients in group A, three in group F, two in group A+V, and four in group F+V, without any significant difference between patients taking or not verapamil), in which external cardioversion failed to restore the sinus rhythm, refused to undergo the internal cardioversion. Thirteen (3.6%) patients were dropped out from the follow-up because of pharmacological side effects: there was no statistically significant difference in the incidence of side-effects requiring the stop of the medication between a single-drug regimen (4/162 patients, 2.5%) and a two-drug regimen (9/162 patients, 5.6%). Only the six patients who stopped the pharmacological therapy before the cardioversion, were not enrolled. So the final study group consisted of 324 patients. As shown in Table 1, there was no significant difference in any clinical characteristics among the four study groups. In Table 2 are shown the concomitant
medication used at time of cardioversion. One again, no difference was observed in the drug distribution among the four study groups.

### Electrical cardioversion

In 321 out of 334 (96.1%) patients external cardioversion restored sinus rhythm with a mean of 1.9±0.8 shocks and a mean cumulative energy of 485±247 J. There was no statistically difference in the mean body surface area and body weight among the several study groups. The mean number of shocks, required to restore the sinus rhythm, was higher in group A as compared to group F (P=0.01), whereas the mean cumulative energy was higher in group A as compared to group F (P=0.001) and group F+V (P=0.02) (Table 3). Among the 13 patients, in which external cardioversion failed to restore the sinus rhythm, only three underwent internal cardioversion and all were converted with a single shock of 5 J. Before the electrical cardioversion, and during the follow-up no embolic events were observed.

### AF recurrences

During the 3 months of follow-up, 89 (27.5%) patients had an AF recurrence. Among them three patients (one group A, one group F, and one group F+V) had both AF and atrial flutter episodes. At univariate analysis verapamil significantly reduced the AF recurrences if added to amiodarone or flecainide (from 35% to 20%, P=0.004). In more detail, whereas the adding of verapamil to flecainide significantly reduced the recurrence of AF (from 38% to 21%, P=0.02), the benefit of adding verapamil to amiodarone did not reached the statistic significance (AF recurrences were reduced from 32% to 20%, P=0.08) Multivariate Cox analysis did not evidenced significant differences between amiodarone and flecainide. Age, sex, left atrial diameter, left ventricle ejection fraction, duration of AF, previous cardioversion, presence of heart disease, concomitant medication used, and antiarrhythmic drugs employed were considered as explanatory variables in the Cox proportional hazards model. Only age, duration of AF, and use of verapamil were significantly retained in the final model after stepwise selection (Table 4). Plots of event free survival curves for patients with and without verapamil therapy, adjusted for mean age (62.2 years) and AF duration (67.8 days) are reported in Fig. 1.

Each of the 89 patients, who had an AF recurrence during the 3 months follow-up period, were switched to the alternative treatment: Twenty-six group A patients received amiodarone plus verapamil, 30 group F patients received flecainide plus verapamil, 16 group A+V patients received amiodarone alone, 17 group F+V patient received flecainide alone. The percentage of secondary AF recurrence were 77%, 57%, 81%, 88%, respectively. The addition of verapamil to group A and F patients, significantly decreased the AF recurrence rate as compared to group A+V and F+V patients who stopped the verapamil therapy (68% vs 88%, P=0.03).

### Discussion

To our knowledge, this is the larger, multicenter, prospective and randomized study to evaluate the...
impact of a pre-treatment with verapamil, combined with a class IC or III antiarrhythmic drug, on AF recurrence in patients undergone electrical cardioversion. In our series the addition of verapamil was effective in reducing the AF recurrences, that were more frequent in older patients and in patients with longer lasting AF. Moreover verapamil significantly reduced the secondary AF recurrences in patients with an AF recurrence within 3 months after cardioversion, and did not affect the energy requirement for obtaining lasting sinus rhythm.

Role of pharmacological pre-treatment in reducing AF recurrences

It has long been known that most recurrences of AF occur within the first month after electrical cardioversion as a result of fibrillation-induced electrical remodelling of the atria. The efficacy of a pre-treatment with class I and class III antiarrhythmic drugs, in preventing acute and sub acute AF recurrences has been reported. Recently the role of the verapamil, alone, or combined with another antiarrhythmic drug have been investigated. Tieleman et al., in an observational study, reported, by the multivariate analysis, that the use of intracellular lowering drugs before cardioversion was the only independent predictor for maintenance of sinus rhythm after successful cardioversion. De Simone et al., in a prospective and randomized study, reported that 6 days of oral verapamil administration centered on the cardioversion day, combined with propafenone, significantly reduce the incidence of early recurrences of AF compared with propafenone alone. Smaller series comparing amiodarone or amiodarone and propafenone, alone or combined with verapamil, did not show any favourable effect of pre-treatment with verapamil in term of prevention of early AF recurrences. Moreover, Van Noord et al. demonstrated that, stand alone, intracellular calcium lowering by verapamil, around electrical cardioversion, does not enhance cardioversion outcome. These conflicting results have several potential explanation: (1) overall number of patients studied is very low (less than 500); (2) clinical characteristic of the patients enrolled ranged widely (i.e. the AF duration ranged from 18 to plus than 500 days); (3) verapamil have been tested alone or combined with amiodarone or propafenone, using several administration protocols (80 mg three times a day, 120 mg twice a day).

To overcome these limitations we designed this multicenter, prospective, randomized trial, in which 363 patients were enrolled. Significantly, in the Cox proportional hazards regression model, only the younger age, shorter duration of AF, and the use of verapamil were predictor of sinus rhythm maintenance after cardioversion. Moreover, verapamil reduced the secondary AF recurrences (from 88% to 68%, P=0.03) in patients with an

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group F</th>
<th>Group A+V</th>
<th>Group F+V</th>
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</thead>
<tbody>
<tr>
<td>Mean body surface area (m²)</td>
<td>1.83±0.4</td>
<td>1.8±0.36</td>
<td>1.81±0.4</td>
<td>1.87±0.44</td>
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<td>Mean body weight (kg)</td>
<td>72±12</td>
<td>71±12</td>
<td>72±11</td>
<td>74±12</td>
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<tr>
<td>Mean number of shocks</td>
<td>2±0.8</td>
<td>1.7±0.7</td>
<td>1.9±0.7</td>
<td>1.8±0.8</td>
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<tr>
<td>Mean cumulative energy (joules)</td>
<td>553±246</td>
<td>427±236</td>
<td>496±246</td>
<td>460±247</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Significance</th>
<th>Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>0.776</td>
<td>0.227</td>
<td>11.708</td>
<td>&lt;0.001</td>
<td>2.173</td>
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<tr>
<td>Duration of atrial fibrillation</td>
<td>0.006</td>
<td>0.001</td>
<td>24.974</td>
<td>&lt;0.001</td>
<td>1.060</td>
</tr>
<tr>
<td>Age</td>
<td>0.023</td>
<td>0.011</td>
<td>4.540</td>
<td>&lt;0.05</td>
<td>1.024</td>
</tr>
</tbody>
</table>

*B=regression coefficient.

SE=standard error of B.

Exp (B)=e^B.
AF recurrence after the first cardioversion, too. The latter data are in accord with two studies which reported the acute and subacute use of verapamil, respectively, immediately after and within 7 days after an electrical cardioversion with an early AF recurrence. In both studies the calcium lowering therapy reduced secondary recurrences of AF, by decreasing the amount of atrial ectopic beats.

Role of pharmacological pre-treatment in reducing defibrillation energy requirements

Antiarrhythmic drugs may influence the defibrillation energy required for AF cardioversion. Although conflicting data have been reported on the impact of class IC and III antiarrhythmic drugs on the defibrillation threshold, the effect of verapamil on defibrillation energy requirements has not been investigated yet. Significantly, in our study, the addition of verapamil to amiodarone or flecainide did not modify the mean number of shocks and the mean cumulative energy required for cardioversion. On the other hand the mean number of shocks and mean cumulative energy were significantly lower in the flecainide group as compared to amiodarone group (P=0.01, and P=0.001, respectively), confirming the favourable effect of flecainide on defibrillation energy requirements, that has been associated to a marked increase of FF interval.

Study limitations

The study has several potential limitations: (1) efficacy of the four antiarrhythmic protocols tested was assessed on the basis of patients’ symptoms, however brief episodes of atrial arrhythmias might be asymptomatic; (2) verapamil, reducing the ventricular rate during AF, could decrease the symptoms related to AF recurrences and the patients’ capability to recognize an AF episode; (3) impact of verapamil alone on primary and secondary AF recurrence has not been investigated; (4) cooperative effect of verapamil and amiodarone is probably less than verapamil and flecainide since amiodarone itself has a week calcium antagonist effect; (5) although all patient enrolled had spontaneous or drug-induced normal blood pressure values, we cannot exclude that the beneficial effect of verapamil may be, partially, due to a better blood pressure control.

Clinical implications

This study suggests that oral verapamil administration, combined with a class IC or III antiarrhythmic drug, is effective in reducing both primary and secondary AF recurrences in patients who undergo electrical cardioversion. Energy requirement for obtaining lasting sinus rhythm is not increased and combined therapy is generally well tolerated, so that it could be considered a valid strategy in patients undergoing electrical cardioversion.

References