INTRODUCTION

Atrial fibrillation (AF) occurs in a large part of the adult population (1) and is closely related to high rates of morbidity and mortality (2). Besides, it has been estimated that patients with AF present a cost for health five times higher than those not suffering from AF. Fifty percent (50%) of the expenditures focus on the direct cost associated with hospitalization in acute phase (3). Therefore, it is desirable to use a strategy with as possible less intervention and hospitalization for treatment (4).

Pharmacological cardioversion of AF is a very common condition for the clinical cardiologist in everyday practice, if the arrhythmia is of recent onset (5). The AF is associated with thromboembolic events and tachycardia-induced cardiomyopathy (6). Early cardioversion reduces the risk of thromboembolic events and relapses of the arrhythmia (7). If the duration of AF is < 48h and the risk of stroke is low, then the cardioversion could be attempted swiftly, with safety, without the need for a transesophageal ultrasound (8). The drug should be effective with a high rate of cardioversion or adjustment of the high rate of arrhythmia, with rapid action and low incidence of side effects (9).

The aim of the study is the evaluation of the efficacy and safety of flecainide per os in patients with recent-onset (<48 hours) AF. The management of patients with recent-onset Atrial Fibrillation (AF) presenting at emergency departments varies widely.

MATERIALS and METHODS

Study Population

Patients were considered as potential candidates for the study if they suffered from sustained AF with a ventricular
rate of over 60 beats per minute at rest and AF of recent onset (<48 hours). Patients who presented with recent-onset AF (one to 48 hours), who were evaluated and decided their arrhythmia to be converted to sinus rhythm were enrolled. We performed a randomized, single-blind trial including 81 hemodynamically stable patients with the following inclusion criteria: the subjects were adults (>18 years old), the AF should not be secondary to structural heart disease, due to coronary artery disease (Coronary Artery Disease was excluded from the medical history, the physical examination, the ECG (absence of any alterations) and the biochemical data. In 4 cases normal coronary arteriography was needed) or symptomatic heart failure (NYHA class II-IV) either hypertrophic cardiomyopathy and should not have any high-grade atrioventricular conduction disorders, such as second-degree heart block (type Mobitz II) or third-degree (complete) heart block either left bundle branch block at their electrocardiogram (ECG) or thyroid dysfunction (hyperthyroidism, hypothyroidism).

Furthermore, patients should not suffer from any kind of chronic kidney disease.

A total of 81 subjects with a recent-onset AF were randomized. They were allocated into two groups and randomization was accomplished by their registry number: odd numbers were allocated to group A, and even numbers to group B). Group A consisted of 41 patients (28 men and 13 women) with a mean age of 64.7 ± 15.67 years. They were administrated p.o.s a single dose of 200 mg flecainide and if necessary another 100 mg after 60 minutes. Group B consisted of 40 patients (26 men and 14 women) with a mean age of 67.5 ± 18.74 years. They were treated only for rate control, if needed. They were administrated beta-blocker, non-dihydropyridine calcium channel antagonists (verapamil or diltiazem) or digoxin.

Medical history, physical examination, laboratory routine, and chest x-Ray were available in all patients. Moreover, in all patients, a transthoracic ECHO was performed and where necessary, a transesophageal ECHO (in 6 patients to exclude the presence of a left atrial appendix thrombus). The heart rate was estimated from the ECG.

Study Design
The primary outcome was the estimation of efficacy and safety of flecainide at 45 minutes, 60 minutes, 3-6 hours, 6-12 hours, 12-24 hours and 24-36 hours after the initial dose. Blood Pressure (BP) was measured via an automatic hand-held manometer per hour. Patients' complaints and side effects were recorded and investigated. Only those related to the medication were estimated.

If the arrhythmia was not terminated after 48 hours from the administration of the flecainide, electric cardioversion was performed.

The primary endpoint for efficacy was time to cardioversion. The safety of flecainide was described by registration and monitoring of side effects.

Statistical Analysis
Collected data analysis was performed using the Statistical package software SPSS version 19.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). Initially, calculation of the normality for the distribution of quantitative variables was made, using the Shapiro Wilks test (data in each group < 50 patients). For comparison of the quantitative variables unpaired t-test and non-parametric Mann-Whitney U test were used, while the x² test and the Fisher test were used to assess differences in the distribution of qualitative variables.

All-time variables until the event (cardioversion of AF) were presented in Kaplan-Meier curves and analyzed by log-rank test, calculating and comparing the rates of cardioversion. Then the univariate relationship of the variables with the combined endpoint (conversion of AF) was examined and variables that showed a significant association were included in a multivariate model analysis (Binary logistic analysis model), where the variables associated with cardioversion of AF could be identified. They were expressed as Odds Ratio (OR) and 95% confidence interval (95% CI) was estimated. The probability p < 0.05 (2-way) was considered statistically significant.

The study protocol was approved by the Scientific Committee of the Hospital (Number 167/2017) according to the Helsinki Declaration, and written consent was obtained from all patients.

RESULTS
Table 1 shows the baseline characteristics of all patients in the study. There is no significant demographic and structural difference between the groups. About three-quarters were hypertensive, while one to three patients were diabetic as well. None of the patients had ischemic heart disease or any significant structural heart disease. The echocardiogram parameters related to patients' heart function, such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD) and left atrial (LA) size were within normal limits. Their mean heart rate at the time of enrolling was above 110 beats per minute. There were no significant differences between patients of the two groups.

Figure 1 shows the exact number of patients that were successfully cardioverted from Group A and Group B at each time period. Out of 81 patients with AF who were enrolled in the study, 37 patients of Group A (90.24%) restored sinus rhythm with p.o. flecainide in 24 hours versus 5 patients of Group B (12.5%). The cardioversion for 27 patients of Group A (72.97%) was managed in the first three hours and most of them were discharged from the hospital. The percentage of patients treated per time is shown in Figure 2.

Binomial logistic regression analysis was performed to identify the variables associated with the successful
cardioversion of AF. The covariates chosen to be included were age, flecainide usage, heart rate, the duration time of the episode and the left atrial size, which on univariate analysis were associated with successful cardioversion. All the above are shown in Table 2.

### Table 1. Baseline characteristics of the patients. There is no significant demographic and structural difference between the groups

<table>
<thead>
<tr>
<th></th>
<th>Group A n=41</th>
<th>Group B n=40</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.7±15.67</td>
<td>67.5±18.74</td>
<td>0.070</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>28 (68.29)</td>
<td>26 (65)</td>
<td>0.140</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>32 (78.04)</td>
<td>30 (75)</td>
<td>0.100</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>12 (29.27)</td>
<td>11 (27.5)</td>
<td>0.100</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.7±18.7</td>
<td>138.3±19.3</td>
<td>0.130</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.4±6.8</td>
<td>81.56±6.96</td>
<td>0.100</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>38.18±6.7</td>
<td>41.34±7.4</td>
<td>0.200</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>54.2±3.6</td>
<td>53.7±4.1</td>
<td>0.700</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.7±2.83</td>
<td>53.5±1.96</td>
<td>0.870</td>
</tr>
<tr>
<td>Rate ventricular response (beats/min)</td>
<td>114.3±29.6</td>
<td>117.2±26.8</td>
<td>0.700</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LA diameter: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction

### Table 2. Predictors of AF successful cardioversion

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR (95% OR)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>-0.027</td>
<td>1.08 (1.04 – 1.093)</td>
<td>0.040</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2.47</td>
<td>11.81 (4.6 – 30.47)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Ventricular Rate</td>
<td>0.98</td>
<td>1.15 (1.02 – 1.48)</td>
<td>0.040</td>
</tr>
<tr>
<td>Episode Duration</td>
<td>-0.15</td>
<td>0.94 (0.89 – 0.99)</td>
<td>0.010</td>
</tr>
<tr>
<td>Left Atrial Size</td>
<td>-0.14</td>
<td>0.87 (0.54 – 0.97)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

On multivariable logistic regression analysis, only the administration of flecainide was an independent factor of successful cardioversion of the atrial fibrillation in 36 hours (OR=3.69 – CI: 3.02-4.68).

All the patients were discharged from the hospital. Those who received flecainide didn’t show up any side effects, such as hypotension, atrial flutter with 1:1 conduction, QT prolongation, dizziness or vision problems (blurred vision, focusing problems, optical spots) during the follow-up period. QRS interval before and after administration of flecainide remained unchanged (97 msec, range 78 to 197 msec). All patients from the rate control group (group B) who were not cardioverted (4 patients denied the electric cardioversion), left the hospital with their heart rate within normal limits and remained asymptomatic.

**DISCUSSION**

In this randomized study the efficacy and safety of p.o.s. administration of flecainide was compared with the rate control schedule in patients with recent-onset AF. The p.o.s. administration of flecainide was more efficacious than rate control and safe as well. According to Framingham Heart Study, lifetime risks for development of AF are 1 in 4 for men and women 40 years of age and older and remains high (1 in 6) even in the absence of antecedent congestive heart failure or myocardial infarction (11). It is also well known that progression from paroxysmal to sustained AF is significantly associated with increased adverse events, such as an increased risk of ischemic stroke or systemic
embolism and hospitalization for heart failure during the periprogression period (12). This is the reason that the preservation of sinus rhythm is meaningful, even if out-of-hospital self-administration of an antiarrhythmic drug is needed after safety has been established in the hospital setting (13). Flecainide, as well propafenone, is used compatible with this approach, not only for in-hospital treatment but also in the so-called “pill-in-the-pocket” strategy for pharmacological cardioversion of AF, to reduce health care utilization (emergency department visits or cardioversions) (14).

A large number of patients with recent-onset AF cardiovert spontaneously in 24-48 hours after the onset of AF. The pharmacological treatment promotes cardioversion to sinus rhythm in patients with recent-onset AF. However, the advantage becomes milder 24-48 hours after the administration of the drug (15). The pharmacological cardioversion is preferred over the electrical because the use of sedation and anesthesia are avoided (16).

The above is confirmed from other studies with the use of p.os. antiarrhythmic drugs (propafenone etc) (17,18) which confirmed the results of our study with oral flecainide.

The economic costs of treating patients with AF are estimated to 1-2.7% of the total annual health expenditure. A significant proportion of these costs is the direct cost associated with hospitalization and acute care (19,20). In a study from USA, patients with AF had an average hospitalization time of 3.9±5.2 days and a mean cost of hospitalization $6692±4928 per patient (21). The change in the cost of strategy in the treatment (p.os. drug administration) seems that reduces the use of health services and the cost.

However, it is important to recognize that only 12% of the patients who arrive at the Emergency Department with AF are candidates for p.os. antiarrhythmic therapy because many of the existed situations could prevent it (4).

Flecainide is ranged to the Ic group in the Vaughan-Williams antiarrhythmic drug classification. It works through impairing sodium movement by inhibiting the fast inward sodium channels in the cell membrane of the heart muscle tissue and this action is more pronounced during faster heart rates (22). Flecainide reduces the number of reentrant circuits, by causing a tachycardia-dependent increase in the atrial effective refractory period, so as the myocardium can no longer preserve the arrhythmia itself. This is the reason flecainide plays an important role in tachyarrhythmias (23,24).

Flecainide has been available in Europe since the early ’80s (22). Several studies have examined the efficacy of oral flecainide for the conversion of recent onset AF to sinus rhythm in the hospital setting (25,26). According to the RHYTHM-AF study, flecainide either oral or intravenously administrated is an effective agent for pharmacological cardioversion of AF, compared with amiodarone or rate control drugs (27). A single-dose, oral loading with flecainide was an acceptable strategy for in-hospital treatment for selected patients, with a high percentage of cardioversion (approximately 75%) within only three hours (28). Comparable outcomes were observed in another study, in which oral administrated flecainide was compared with i.v. amiodarone (29). The success of the single oral dose of flecainide (300 mg) in cardioversion of recent-onset AF was from 57% to 68% in 2-4 hours and 75% to 91% in 8 hours after administration (25), findings that were proportional to our study. It is widely known that absorption of orally administered flecainide is slow with peak plasma drug levels reached at an average of 3 hours (1 hour – 6 hours), where the drug could be active enough to exert its antiarrhythmic actions (30).

The conversion rate of flecainide is similar to oral propafenone, approximated about 80% at eight hours (31). Moreover, from two other studies in which flecainide was administrated intravenously, the conversion rate was not found to be different, compared with those of p.os flecainide (32,33). Most of the patients could be discharged from the hospital within a few hours without any significant adverse event. Our results were comparable concerning the cardioversion time and the safety profile of flecainide with all the above studies.

Despite the fact of safety and efficacy of flecainide when administrated in the emergency room or in the cardiology ward, the out-of-hospital self-administration of the pill does not seem to predict adverse effects (34). It needs to be a careful choice of those patients that could take p.os. flecainide, to be protected from possible future AF recurrences. The “pill-in-the-pocket” approach, using p.os. flecainide, is quite well tolerated and it’s a safe option! for patients suffering from symptomatic AF (35).

The adverse effects are uncommon, particularly rapid atrial flutter, ventricular tachycardia, intraventricular conduction disturbances, hypotension and bradycardia at the time of conversion. They were not observed in the patients of our study. The drug, however, should be used with caution and avoided in patients with heart failure or severe chronic obstructive pulmonary disease (36,37). The guidelines advise that the first p.os. administration of flecainide should be tried in a monitoring environment. Moreover, a previous successful administration of the drug will not exclude future events (8).

**LIMITATIONS**

Limitations of the study: We did not perform a comparison with the placebo, because many studies have demonstrated the superiority of flecainide over placebo during the follow-up period. Our purpose was to investigate the possibility of administration of the drug p.os., efficacy and safety during the short follow-up period. In addition, we preferred to exclude the incidental effect, that was the comparison with the rate control.

**CONCLUSION**

In carefully selected patients presenting with recent-onset AF and without structural heart disease the use of flecainide per os has shown significant efficacy for cardioversion and has a low incidence of adverse effects.


REFERENCES


Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The study protocol was approved by the Scientific Committee of the Hospital (Number 167/2017) according to the Helsinki Declaration.


