Pharmacological conversion of recent atrial fibrillation: a randomized, placebo-controlled study of three antiarrhythmic drugs

Yeni başlayan atriyal fibrilasyonun ilaçla sinüs ritmine döndürülmesi: Üç antiaritmik ilaçla gerçekleştirilen randomize, plasebo-kontrollü çalışma

Idriz Balla, Elizana Petrela, Anesti Kondili*

From Departments of Cardiology and *Public Health, University Hospital Center of Tirana, Tirana-*Albania*

ABSTRACT

Objective: In this study, we randomly compared single oral doses of flecainide, amiodarone and propafenone versus placebo for the conversion of recent atrial fibrillation (AF) (within 48 hours).

Methods: This is a randomized prospective, placebo-controlled single-blind study that included 160 consecutive patients with recent AF who were randomly assigned to single oral doses of flecainide (3 mg/kg of weight, n=40), amiodarone (30 mg/kg weight, n=40), propafenone (8.5 mg/kg of weight, n=40) or placebo (n=40). The primary end-point was conversion rate at 24 hours after the drug intake. The association between antiarrhythmic use and conversion rate was tested with multiple logistic regressions.

Results: The primary end-point was achieved in 87.5% of patients with flecainide, 85% of patients with amiodarone, 85% of patients with propafenone and 17.5% of patients with placebo ($p<0.001$ compared with placebo for all 3 drugs). Conversion rate within 3 hours after drug intake was greater with propafenone (57.5%) or flecainide (45%) compared with amiodarone (0%) or placebo (10%). Between 6 and 24 hours, significantly more patients were converted to sinus rhythm with amiodarone than with flecainide or propafenone. The use of antiarrhythmic drugs was a significant predictor of conversion to sinus rhythm compared to placebo (adjusted OR=19.53, 95% CI 3.14-121.55, $p<0.001$). No serious side effect occurred.

Conclusion: In patients with recent-onset AF, oral flecainide, amiodarone or propafenone are superior to placebo in restoring sinus rhythm within the 24-hour period following the drug intake. *(Anadolu Kardiyol Derg 2011; 11: 600-6)*

Key words: Amiodarone, atrial fibrillation, flecainide, propafenone, sinus rhythm, logistic regression analysis

ÖZET

Amaç: Atriyal fibrilasyonun (AF) sinüs ritmine döndürülmesi çoğu kez emboli riskini ve hemodinamik bozulmanın azaltılması için yapılır. Bu çalışmada, son 48 saat içinde AF geçirmiş hastalar üzerinde tek oral doz flekainid, amiyodaron ve propafenon ile atriyal fibrilasyonun sinüs ritmine dönüşümü üzerindeki etkileri plasebo ile randomize olarak karşılaştırılmıştır.

Yöntemler: Bu çalışma 160 hasta üzerinde yapılmış, hastalara rastgele olmak üzere flekainid (3 mg/kg, n=40), amiyodaron (30 mg/kg, n=40), propafenon (8.5 mg/kg, n=40) veya placebo (n=40) verilmiştir. Amaçlanan nokta ilaç alınımı sonrası 24 saat içinde AF'nin sinüs ritmine dönüşüm hızı olmuştur. AF konversiyon oranı ile 3 antiaritmik ilacın kullanımı ile ilişkiler çoklu lojistik regresyon analiz ile değerlendirilmiştir.

Bulgular: Amaçlanan etki, flekainid kullanan hastaların %87.5'inde, amiyodaron kullanan hastaların %85'inde, propafenon kullanan hastaların 85%'inde, plasebo kullanan hastaların ise %17.5'inde ($p<0.001$ her 3 ilacın plasebo ile karşılaştırılması) gerçekleşmiştir. İlaç alımından 3 saat sonraki dönüşüm hızı, amiodaron (%0) ve plasebo (%10) ile karşılaştırıldığında; Propafenon grubunda (%57.5) ve flekainid grubunda (%45) olmak üzere daha yüksek bulunmuştur. Amiyodaron kullanan hastalar 6 ve 24 saat içinde, flekainid veya propafenon grubu hastalara göre anlamlı olarak daha fazla sinüs ritmine döndürülmüştür. Plasebo ile kıyaslandığında antiaritmik ilaçların kullanımı sinüs ritmine dönüştürmede belirgin derecede üstün bulundu (düzeltilmiş OR=19.53, %95 GA 3.14-121.55, $p<0.001$). Önemli yan etki gözlenmedi.

Sonuç: Atriyal fibrilasyona yakın zamanda girmiş hastalarda oral ilaç alımını izleyen 24 saatlik süreç içinde sinüs ritmine geri döndürmede flekainid, amiyodaron veya propafenon grubu, plasebo grubuna göre üstün bulunmuştur. Propafenon ve flekainid'in oral alım sonrası ilk 3 saat içinde amiyodaron'a göre daha etkili olmakla birlikte her 3 antiaritmik ilaç benzer etkinliktedir. *(Anadolu Kardiyol Derg 2011; 11: 600-6)*

Anahtar kelimeler: Amiyodaron, atriyal fibrilasyon, flekainid, propafenon, sinüs ritm, lojistik regresyon analizi

Address for Correspondence/Yazışma Adresi: Idriz Balla, MD, Department of Cardiology, University Hospital Center of Tirana, Tirana-*Albania* Phone: 00 355 42 22 54 66 Fax: 00 355 42 22 54 66 E-mail: idrizballa@yahoo.com

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Introduction

Pharmacological conversion of atrial fibrillation (AF) to sinus rhythm is commonly attempted. Ideally, the pharmacological treatment should have a high conversion rate or be able to control the improper high ventricular rate, be rapid in action and have a low incidence of side effects. The class IA, IC and III antiarrhythmic drugs have been used as oral therapy to convert AF of recent onset (1, 2). The class IC agents, flecainide and propafenone, have the advantage of acting rapidly, and their efficacy in converting atrial fibrillation of recent onset to sinus rhythm has been documented. Both drugs had a similar efficacy with the success rates ranging from 58% to 95% (1-3). Amiodarone has been administered intravenously for the treatment of AF in different doses and the conversion rates ranged from 41% to 100%. High dose oral loading (30-50 mg/kg) of amiodarone has been reported to produce evident electrophysiological effects, suppress supraventricular and ventricular arrhythmias within the first 24 hours after administration, and to be relatively well tolerated (3-5). It has been recently shown that amiodarone as a single oral dose restored sinus in 64% of patients with atrial tachyarrhythmias, having a similar efficacy with intravenous use. However, the studies were not randomized or placebo-controlled (3-5).

The purpose of this randomized study was to compare the efficacy of 3 commonly used and orally administered antiarrhythmic drugs - propafenone, flecainide and amiodarone -in patients with AF of recent onset.

Methods

Study design and sample size

The study was designed as randomized prospective, placebo-controlled single-blind study.

Sample size was calculated on the basis of an expected conversion rate of 75% with antiarrhythmic drugs and a spontaneous conversion of 50% and the requirement for the study to have 80% power at a 2-sided alpha of 0.05. Under these conditions, 37 patients per group were needed.

Study population

This randomized prospective, placebo-controlled single-blind study included 160 consecutive patients with recent AF (within 48 hours from the episode onset). The diagnosis of recent AF was made according to recent guidelines (6). Between October 2006 and December 2008, 370 patients with AF were admitted to the Emergency Department of the University Hospital Center in Tirana. Patients with uncontrolled congestive heart failure, acute myocardial infarction within 7 days, previous electrocardiographic documentation of atrioventricular block or sick sinus syndrome, patients on antiarrhythmic therapy at the time of admission, patients with prior thromboembolic episodes or stroke, patients with impaired hepatic or renal function, patients with advanced obstructive bronchopulmonary disease or pregnancy were excluded.

After exclusion of patients with above-mentioned conditions, 160 patients with AF remained and were included in this study.

The study has been carried out in accordance with the Declaration of Helsinki and has been approved by the institutional Ethics Committee. An informed consent was obtained from all patients.

Baseline clinical examinations

The diagnosis of AF was established based on 12-lead electrocardiogram (ECG) criteria (absence of p waves, presence of irregular atrial electrical activity and irregular RR intervals). Mean age of the patients was 58.1±10.3 years. Medical history, physical examination, routine biochemical data and thoracic X-ray examination were obtained in every patient. All patients underwent transthoracic and transesophageal echocardiography to rule out the presence of atrial thrombi. Heart rate was taken from ECGs. Left atrial dimensions and parameters of left ventricular function were obtained from echocardiograms. Patient's weight was measured to allow dose calculations of antiarrhythmic drugs per kilogram of weight. No anticoagulants or antithrombotic drugs with the exception of aspirin were used.

Randomization process and protocol of drug application

After diagnosis of AF of recent onset was made in the Emergency Department, patients were transferred to the coronary care unit. Antiarrhythmic drugs and placebo were coded with numbers (from 1 to 4) and placed in an envelope. Upon patients' arrival in the coronary care unit, patients were randomly assigned (based on withdrawal of numbers from the envelope) to single oral doses of amiodarone (30 mg/kg of weight; n=40 patients), flecainide (3 mg/kg of weight; n=40 patients), propafenone (8.5 mg/kg of weight; n=40 patients) or placebo (n=40 patients). The study was single-blind (on the patients' side). Conversion to SR was verified by 24-hour monitoring. The monitoring and end-point adjudication were performed by personnel who were unaware of the type of the drug. The results of therapy were assessed at 3, 6, 12 and 24 hours after the drug intake. No other rate control drugs were used in any of the randomization groups. Diagram of the flow of study participants through each randomization process was constructed according to the CONSORT (Consolidated Standards of Reporting Trials) statement (7).

Primary end-point

The primary end- point of the study was conversion rate at 24 hours after drug intake.

Monitoring of efficacy and side effects

Patients underwent continuous electrocardiographic monitoring for at least 24 hours. Moreover, 12-lead electrocardiograms were recorded before drug ingestion and at 3, 6, 12 and 24 hours

thereafter. Blood pressure was hourly measured with the mercury sphygmomanometer. To evidence any possible side effects from the drug intake, patients' complaints were carefully searched for and recorded. Electrocardiographic documentation of the stable sinus rhythm was required to evidence conversion of atrial fibrillation to sinus rhythm. Heart rate and eventual organization to other regular atrial arrhythmias were also documented.

Statistical analysis

Analysis was performed with the SPSS Statistical Package (version 15; SPSS Inc, Chicago, Illinois).

Data are expressed as mean±SD for continuous variables or proportions (percentages). Continuous variables (all continuous variables had a normal distribution) were compared with one-way analysis of variance (ANOVA). Chi-square test was used for comparison of discrete variables. Multiple logistic regression models were applied to identify the independent correlates of conversion to sinus rhythm within the 24 hours after drug use (dependent variable). All variables of Table 1 were included into the analysis (independent variables). A two-sided p value of <0.05 was considered to indicate the statistical significance.

Results

Baseline characteristics

The flow diagram of the study participant's recruitment is shown in Figure 1. The study included 160 patients with AF. Of them, 40 patients were randomly assigned to amiodarone, 40 patients to flecainide, 40 patients to propafenone and 40 patients to placebo.

Baseline characteristics of the patients are shown in Table 1. There were no significant differences between patients regarding baseline characteristics.

Conversion rates (Table 2)

Within the first 3 hours, propafenone (conversion rate 57.5%) and flecainide (conversion rate 45%) restored sinus rhythm significantly more often than placebo (p<0.001 for both comparisons) or amiodarone (0%, p<0.001 for both comparisons). There were no significant differences in conversion rates between propafenone versus flecainide (p=0.73).

In the interval from 3 to 6 hours, 11 additional patients in flecainide group (27.5%), 5 patients in the amiodarone group (12.5%), 6 patients in propafenone group (15.0%) and 3 patients in the placebo group (7.5%) were converted to sinus rhythm.

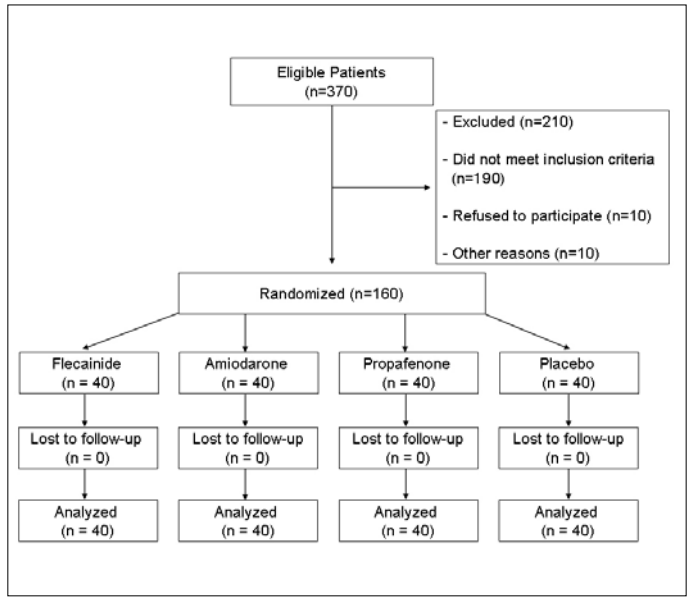

Figure 1. Diagram showing the flow of study participants through each randomization process

Table 1. Patients' baseline characteristics

Variables	Flecainide (n=40)	Amiodarone (n=40)	Propafenone (n=40)	Placebo (n=40)	F	p*
Age, years	57.9± 9.5	58.9±10.4	57.4±9.8	58.6±10.7	0.997	0.075
Males/Females, n	28/12	29/11	20/25	24/16	-	0.142
Arterial hypertension, n	18/22	12/28	20/20	9/31	-	0.165
Diabetes mellitus, n	10/30	16/24	12/28	8/32	-	0.436
Systolic blood pressure, mmHg	120.0±10.9	127.3±6.0	131.1±15.5	131.7±8.5	0.784	0.109
Diastolic blood pressure, mmHg	73.4±7.0	75.5±7.1	81.3±7.2	76.5±7.5	0.863	0.113
Duration of last AF episode, hours	16.2±9.1	19.1±12.4	18.6±4.2	17.8±13.9	0.993	0.136
Potassium, mEq/l	3.86±0.23	4.04±0.27	3.62±1.22	4.70±0.60	0.789	0.112
LA diameter, mm	36.1±3.2	42.3±4.3	34.4±5.3	32.9±6.3	0.892	0.256
LV end-diastolic diameter, mm	55.1±2.0	50.7±3.7	51.4±4.8	48.4±4.8	0.894	0.065
% of LV fractional shortening	33.3±2.6	31.5±3.4	34.6±4.5	34.4±4.2	0.877	0.357
Ventricular rate, bpm	116.2±28.2	119.4±27.9	117.6±35.2	145.5±27.9	0.999	0.055

Data are presented as mean±SD and proportions
*one-way ANOVA and Chi-square test
AF - atrial fibrillation, LA - left atrium, LV - left ventricle

Conversion rates at 6 hours are shown in Table 2. Both flecainide and propafenone were superior to amiodarone or placebo at this time interval. Between 6 and 12 hours 5 additional patients in the flecainide group (12.5%), 18 patients in the amiodarone group (45%), 3 patients in the propafenone group (7.5%) were converted to sinus rhythm. At this time interval amiodarone was superior to other 2 antiarrhythmics and placebo regarding conversion rate. Between 12 and 24 hours, 1 additional patient in flecainide group (2.5%), 11 patients (27.5%) in the amiodarone group and 2 patients in the propafenone group (5.0%) were converted to sinus rhythm. Again amiodarone was superior to flecainide or propafenone with respect to conversion rate between 12th and 24th hours from drug administration (Fig. 2).

At the end of 24-hour monitoring period, the primary endpoint was achieved in 87.5% of patients assigned to flecainide, 85% of patients assigned to amiodarone, 85% of patients assigned to propafenone and 17.5% of patients assigned to placebo (p<0.001). All three drugs were superior to placebo regarding the conversion rate. No differences were observed between all three antiarrhythmic drugs (p=0.75). After conversion to sinus rhythm, no recurrences of atrial fibrillation were observed during the monitoring time (up to 24 hours after randomization).

Patients still in atrial fibrillation after 24 hours from randomization were anticoagulated with warfarin and scheduled to undergo cardioversion 3 to 4 weeks thereafter.

Predictors of AF conversion to sinus rhythm (Table 3)

Multiple logistic regression models were used to identify the independent correlates of AF conversion within the 24 hours from the treatment onset The use of antiarrhythmic drugs, age, duration of AF episode and heart rate were independent predictors of conversion to sinus rhythm within the first 24 hours after randomization (p<0.001, p=0.003, p<0.001 and p=0.035, respectively).

Side effects

There were no significant adverse effects during the follow-up period in the drug treatment arm. Two patients in the amiodarone group had mild diarrhea.

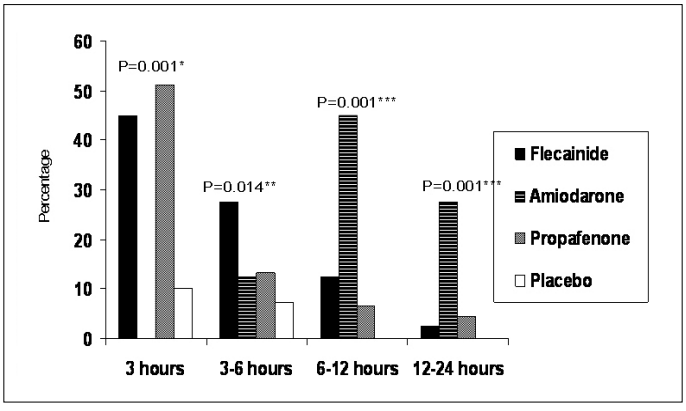

Figure 2. Percentage of patients converted to sinus rhythms in various time intervals. *=flecainide vs. placebo; **=flecainide vs. placebo; *=amiodarone vs placebo or flecainide or propafenone**

Table 2. Conversion rate in various time intervals

Variables	Flecainide (n=40)	Amiodarone (n=40)	Propafenone (n=40)	Placebo (n=40)	p*
Conversion rate, n(%)					
At 3 hours	18 (45)*	0	23 (57.5)	4 (10)	<0.001
At 6 hours	29 (72.5)	5 (12.5)	29 (72.5)	7 (17.5)	0.036
At 12 hours	34 (85)	23 (57.5)	32 (80.0)	7 (17.5)	0.001
At 24 hours	35 (87.5)	34 (85)	34 (85.0)	7 (17.5)	<0.001
Unconverted at 24 hours, n (%)	5 (12.5)	6 (15)	6 (15)	33 (82.5)	<0.001
Heart rate at sinus rhythm, beats/min	79±6	74±9	76±15	84±9	0.09

Data are numbers of patients and percentage
*Chi-square test and one-way ANOVA

Table 3. Predictors of AF conversion to sinus rhythm

Variables	Adjusted odds ratio* [95% confidence interval]	p*
Age (for 10-year increase in age)	0.34 [0.17 - 0.70]	0.003
Male sex	0.61 [0.20 - 1.85]	0.386
AF duration (for 1 hour increase in duration)	0.89 [0.85-— 0.94]	<0.001
Arterial hypertension	0.68 [0.41 - 1.24]	0.156
Diabetes	0.63 [0.27 - 1.23]	0.223
Potassium level (for 1 mg increase)	1.18 [0.22 - 6.33]	0.846
LA diameter (for 7 mm increase)	0.76 [0.34 - 1.69]	0.497
LV end-diastolic diameter (for 7 mm increase)	0.90 [0.33 - 2.50]	0.844
Percentage of LV fractional shortening (for 5% decrease)	0.57 [0.24 - 1.36]	0.204
Heart rate (for 10-beat increase)	1.24 [1.01 - 1.53]	0.035
Use of antiarrhythmic drugs (versus placebo)	19.53 [3.14 - 121.55]	<0.001

*Multiple logistic regression analysis
AF - atrial fibrillation, LA - left atrium, LV - left ventricle

Discussion

In this randomized study, we compared the efficacy and safety of three oral antiarrhythmic drugs in patients with recent onset AF. Our study showed that oral flecainide, propafenone or amiodarone were superior to placebo in conversion of AF to sinus rhythm within the first 24-hour of drug use. There were no differences between the drugs regarding the conversion rate during the 24-hour monitoring period. We observed that the conversion rate within the first three hours in patients who received propafenone group (57.5%) or flecainide (45%) was significantly greater than the conversion rates in groups with amiodarone

(0%) or placebo (10%). Beyond 6 hours, the efficacy of amiodarone was markedly increased with the majority of conversions occurring between 6 and 12 hours after the drug intake. Superiority of amiodarone over flecainide or propafenone was maintained in the 12th to 24th hours interval, as well. The present study showed also that all 3 drugs were safe and well tolerated.

The conversion of AF of recent onset to sinus rhythm is almost always attempted to reduce the risk of embolism and hemodynamic deterioration, unless there are particular reasons to believe that attempts to restore sinus rhythm might be futile or hazardous. In hemodynamically stable patients, the pharmacological intervention to restore sinus rhythm is preferred. The drug selection is mostly empirical or based on limited experience from comparative studies (8). In the recent studies, antiarrhythmic drugs of Vaughan Williams classes IC and III have been used with increasing frequency because of high and consistent therapeutic result (8, 9). The evaluation of drug efficacy by comparing different studies is difficult because of differences in study population characteristics and methodologies including underlying heart disease, duration of arrhythmia, dose and route of drug administration, the monitoring time and, the study endpoints. Pharmacological cardioversion seems to be mostly effective when initiated within first week of the onset of an AF episode (10, 11). A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 hours after AF onset (12, 13).

Pharmacological therapy may promote sinus rhythm restoration in patients with recent-onset AF; however, the advantage over placebo is modest after 24 to 48 hours and the drug therapy is much less effective in patients with persistent AF. Some drugs have a delayed onset of action, and conversion may not occur until several days after treatment initiation (14). Some studies have shown that drug treatment abbreviates the interval to cardioversion compared with placebo without affecting the proportion of patients in whom sinus rhythm is restored after 24 hours (15).

Five meta-analyses of trials compared amiodarone to placebo or other drugs for conversion of recent-onset AF and their results are contradictory (16-20). One meta-analysis reported that amiodarone was effective in restoring sinus rhythm but its use was associated with adverse reactions (16). Another meta-analysis concluded that intravenous amiodarone was no more effective than placebo in restoring sinus rhythm (18). Amiodarone was found to be inferior to type IC drugs for up to 8 hours, but with no difference to these drugs at 24-hour, indicating delayed conversion with the drug (19). In another meta-analysis of 21 trials involving heterogeneous populations, the relative likelihood of achieving sinus rhythm over a 4-week period with oral/intravenous amiodarone was 4.33 in patients with AF of less than 48-hour duration and 1.40 in those with AF of longer than 48-hour duration (20). Because safety data are limited, randomized trials are needed to assess the benefit of amiodarone for conversion of recent-onset AF in specific patient populations. In the SAFE-T trial involving 665 patients with persistent AF, conversion occurred in 27% of patients after 28 days of treatment with amiodarone, compared with 24% with sotalol and 0.8% with placebo (21). Apart from intravenous drug therapy for recent onset AF (within 24-hours), antiarrhythmic agents may also be given over a longer period of time in an effort to achieve cardioversion after a longer periods of AF. Under these circumstances, administration of oral amiodarone is associated with a conversion rate between 15% and 40% over 28 days (14-24). Serious toxicity has been reported, including death due to bradycardia ending in cardiac arrest (10, 24-26).

In placebo-controlled trials, flecainide administered orally or intravenously was effective for cardioversion of recent-onset AF. In 7 studies, the success of a single oral loading dose (300 mg) for cardioversion of recent-onset AF ranged from 57% to 68% at 2 to 4-hours and 75% to 91% at 8-hours after drug administration (27). Single oral loading and intravenous loading regimens of flecainide were equally efficacious, but a response usually occurs within 3 hours after oral administration and 1-hour after intravenous administration. Arrhythmias, including atrial flutter with rapid ventricular rates and bradycardia after conversion, are relatively frequent adverse effects. Transient hypotension and mild neurological side effects may also occur. Overall, adverse reactions are slightly more frequent with flecainide than with propafenone and these drugs should be avoided in patients with underlying organic heart disease involving abnormal ventricular function (27-33).

Placebo-controlled trials have reported that propafenone, given orally or intravenously, is effective for pharmacological cardioversion of recent onset AF. The effect occurs between 2 and 6 hours after oral administration and earlier after intravenous injection, so that when compared with the intravenous regimen, oral propafenone resulted in fewer conversions in the first 2 hours. In 12 placebo-controlled trials, the success rate of oral propafenone (600 mg) for cardioversion of recent-onset AF ranged from 56% to 83% (34). Oral propafenone was as efficacious as flecainide but superior to oral amiodarone and quinidine plus digoxin (15, 35). Limited data suggest reduced efficacy in patients with persistent AF, in patients with atrial flutter, and in patients with structural heart disease. Adverse effects are uncommon but include rapid atrial flutter, ventricular tachycardia, intraventricular conduction disturbances, hypotension, and bradycardia at conversion. Available data on the use of various regimens of propafenone loading in patients with organic heart disease are scant. This agent should be used cautiously or not at all for conversion of AF in such patients and should be avoided in patients with heart failure or severe obstructive lung disease (28, 31, 33, 34, 36-38).

Study limitations

As stated in the study protocol, we used oral therapy to convert to sinus rhythm and patients were hemodynamically stable. As a result, this therapeutic option might be not optimal for patients with hemodynamic instability who may require a rapid-

ly-acting intravenous therapy for frequency control or electrical cardioversion. Moreover, considering the negative inotropic effects of flecainide and propafenone, caution is warranted for the use of such therapy in patients with impaired left ventricular function or overt congestive heart failure. Although, the duration of the last AF episode was accurately measured, the history of AF episodes could not be estimated. The left ventricular ejection fraction was assessed by using the percentage of fractional shortening and not the left ventricular ejection fraction. Finally, the list of variables adjusted for in the multivariable model did not include some known confounders based on the prior studies. Considering the strength of association between the use of antiarrhythmic drugs and conversion to sinus rhythm, adjusting in multivariable model for additional confounders is not expected to override the impact of antiarrhythmic use on AF conversion.

Conclusion

This randomized study demonstrated that flecainide, amiodarone and propafenone are highly effective in converting AF of recent onset to sinus rhythm within the first 24 hours after single dose oral intake. All 3 drugs had similar conversion rates (85 to 87.5%) and were superior to placebo in restoring sinus rhythm within the first 24 hours following oral intake. Propafenone and flecainide appear to be more advantageous than amiodarone within first 6 hours and amiodarone converted more patients to sinus rhythm than flecainide or propafenone in the time interval between 12th and 24th hours. All three drugs were safe and well tolerated in doses used in this study.

Conflict of interest: None declared.

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