Propafenone added to ibutilide increases conversion rates of persistent atrial fibrillation

Panagiotis Korantzopoulos, MD,1,2§  Theofilos M. Kolettis, MD, PhD,1,8
Athanasios Papathanasiou, MD,1  Katerina K. Naka, MD, PhD,1
Panagiotis Kolios, MD,1  Ioannis Leontaridis, MD,1  Antonios Draganigos, MD,3
Christos S. Katsouras, MD, PhD,1  John A. Goudevenos, MD, FESC, FACC1

§ Both authors contributed equally to this work

1Department of Cardiology, University of Ioannina Medical School, 45110 Ioannina, Greece
2Department of Cardiology, ‘G.Hatzikosta’ General Hospital of Ioannina, 45001 Ioannina, Greece
3Department of Cardiology, General Hospital of Corfu, Corfu Island, Greece

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Correspondence to: Dr. Panagiotis Korantzopoulos, Department of Cardiology, University of Ioannina Medical School, 45110 Ioannina, Greece
Tel: +30-26510-45654; Fax: +30-26510-97017
E-mail addresses: pkor@oneway.gr, pan-kor@mailbox.gr
Abstract

Background: Pharmacological conversion of persistent atrial fibrillation (AF) is associated with modest success rates, but combined antiarrhythmic regimens have not been well studied.

Objective: To assess the efficacy and safety of pharmacological conversion of persistent AF with a combined propafenone plus ibutilide regimen.

Methods and results: One hundred consecutive patients (66 male, age 65±10 years) with persistent AF (mean duration 99±92 days) admitted for elective pharmacological cardioversion, were randomly assigned to either treatment with intravenous ibutilide (1 mg plus additional 1 mg, if required) (n=51) or oral propafenone (600 mg) plus intravenous ibutilide at the same dosage (n = 49). Success rates were 41.1% (21 of 51 patients) for ibutilide alone and 71.4% (35 of 49 patients) for propafenone plus ibutilide (p = 0.0044). However, cardioversion occurred earlier in the former group (55±20 min), compared to the latter group (81±32 min, p=0.0019). A comparable increase in the QTc interval was observed in both groups, but one case of sustained torsade de pointes, requiring electrical cardioversion was observed in the propafenone plus ibutilide group. No other complications were noted during the hospitalization period.

Conclusion: Concurrent administration of propafenone plus ibutilide for pharmacologic cardioversion of persistent AF is safe and significantly more effective compared to ibutilide alone.
INTRODUCTION
Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, with an increasing prevalence over the past few decades.\(^1,2\) Although control of the ventricular response may be an acceptable treatment in certain subgroups of patients, restoration and maintenance of sinus rhythm remains the preferred strategy in many patients.\(^3\) This strategy offers several potential benefits, such as prevention of electrical and structural remodeling of the atria, improved haemodynamics, amelioration of symptoms and improvement in the quality of life.\(^3,6\) If this strategy is favored, most patients are managed with electrical cardioversion, because the pharmacological conversion of persistent AF of relatively long duration is often ineffective.\(^7,8\) However, pharmacological conversion obviates the need for general anaesthesia and may be associated with lower peri-procedural complications and increased cost-efficacy.\(^9,10\) Therefore, the development of effective therapies for pharmacological conversion of persistent AF is appealing.

Propafenone and ibutilide are two of the most effective antiarrhythmic agents for cardioversion of acute-onset AF, but their efficacy in cases of persistent AF of long duration is modest.\(^7,8,11-13\) We hypothesized that the combination of these two agents with different pharmacological profiles could improve the success rates in such cases. In the present study, we compared the efficacy and safety of treatment with propafenone plus ibutilide, versus ibutilide alone, on cardioversion of persistent AF.

METHODS
Study population
Consecutive patients >18 and <80 years of age, scheduled for elective pharmacologic cardioversion of persistent AF were screened, and those with duration of the arrhythmia (determined by available electrocardiograms) of over one month but less than one year, were considered eligible for the study. Furthermore, no previous attempts for pharmacological or electrical cardioversion had been performed. The study protocol complies with the Declaration of Helsinki and was approved by the Institutional Ethics’ Committee. All patients underwent clinical assessment, transthoracic two-dimensional and Doppler echocardiographic studies, and laboratory investigations. Patients with thyroid dysfunction (including subclinical hyperthyroidism, defined as TSH below 0.5 µIU/ml), significant valvular heart disease, left atrial diameter greater than 55mm, advanced heart failure (NYHA class III or IV) or left ventricular ejection fraction less than 0.40 were excluded. Exclusion criteria were also acute pericarditis, recent acute coronary event or revascularization, recent infection, malignancies, autoimmune or inflammatory diseases, severe asthma or chronic obstructive pulmonary disease, renal failure, or hepatic failure. Patients with pacemakers, sick sinus syndrome, conduction disturbances, known preexcitation, history of ventricular arrhythmias or torsade de pointes, QTc over 500 msec, systolic blood pressure lower than 90mmHg, electrolyte disturbances or concurrent intake of QT-prolonging drugs were also excluded.

All patients were fully anticoagulated with acenocumarol, targeting at an international normalized ratio of above 2.5, for a minimum of 3 weeks prior to hospital admission. Heart rate was controlled with beta-blockers, diltiazem, digoxin or any combinations of these medications.

Study protocol
The patients were admitted approximately twenty-four hours prior to the scheduled cardioversion and all medications except anticoagulants were discontinued. Clinical assessment was repeated and informed consent was obtained. Randomization was
performed in one to one fashion to either ibutilide or to propafenone plus ibutilide. Treatment in the first group consisted of ibutilide, given at an initial dose of 1 mg intravenously for 10 min and a second dose of 1 mg, administered 10 min after cessation of the first dose, if this was ineffective. Treatment in the second group consisted of 600 mg oral propafenone, followed by intravenous ibutilide, at the same dosage as in the first group. To coincide the onset of action of propafenone (which is approximately 90 minutes after oral intake) with the maximal pharmacologic effect of ibutilide (reported to be approximately 40 minutes after cessation of the infusion) oral propafenone preceded ibutilide administration by 20 minutes. The infusion of ibutilide had been scheduled to be terminated in case of serious dysrhythmias or conduction disturbances. All patients were continuously monitored in the Coronary Care Unit for at least 6 hours after treatment. A 12-lead electrocardiogram at a paper speed of 25 mm/sec was obtained at baseline, 5 minutes after the infusion of the first dose and 5 minutes after the infusion of the second dose of ibutilide (if required), and at 1-hour time intervals thereafter, until the end of the 6-hour observation period. A 12-lead electrocardiogram was repeated 24 hours after drug administration and the conversion was considered successful when sinus rhythm was present. Patients who successfully converted to sinus rhythm were subsequently discharged from the hospital, while those who failed to restore sinus rhythm were scheduled for electrical cardioversion on the next day. Oral treatment for the prevention of AF recurrences (sotalol, amiodarone or propafenone initiated on the second day after cardioversion) was left at the discretion of the referring physician.

One experienced cardiologist blinded to the patients' characteristics and outcome analyzed all electrocardiograms. The QT interval was measured as the interval in milliseconds between the first deflection of QRS and the point of return of the T wave to the isoelectric line. Measurements were obtained from three consecutive complexes in each lead and the resulting average was finally accepted. The leads in which the end of the T wave could not be identified with certainty were excluded from analysis. When a prominent U wave was present, the nadir between T and U waves was considered as the end of T wave. QT interval, corrected for heart rate (QTc), was calculated using the Bazett's formula (QTc = QT/√RR). To assess intraobserver variability, the baseline and post-cardioversion electrocardiogram tracings of 10 randomly selected patients were re-examined 10 days after the initial evaluation and intraobserver variation was less than 5%.

Statistical analysis
Continuous variables are expressed as mean ± one standard deviation and were compared using t-test for independent variables. Categorical variables are expressed as percentages and were compared using chi square, after Yates’ correction. Differences within groups were compared using t-test for dependent variables. All analyses were performed using the 'Statistica 6.0' software program (StatSoft Inc., Tulsa, OK, USA). Statistical significance was defined as an alpha level of 0.05.

RESULTS
Patient characteristics
The study population consisted of 100 patients (66 male, mean age 65±10 years) having persistent AF, of a mean duration of 99±92 days, with a median of 60 days. The clinical and demographic characteristics, as well as the echocardiographic findings were comparable between the two groups (Table 1).

Restoration of sinus rhythm
Sinus rhythm was restored in 21 of 51 patients (41.1%) in the ibutilide group and in
35 of 49 (71.4%) patients in the propafenone plus ibutilide group. This difference was highly significant (p = 0.0044). No patient in the propafenone plus ibutilide group converted to sinus rhythm before the infusion of ibutilide, and one patient in the ibutilide group converted 18 minutes after the onset of the infusion and did not require a second dosage. Cardioversion occurred earlier (p=0.0019) in the ibutilide group (55±20 min after the onset of ibutilide administration), compared to the ibutilide plus propafenone group (81±32min after the onset of ibutilide administration). Timing of conversion to sinus rhythm in the latter group displayed two distinct peaks at 50 and 110 minutes after the onset of ibutilide administration (figure 1). No relapses of AF were recorded in either group during the 24-hour hospitalization period. Moreover, no statistically significant differences in demographic and clinical characteristics were found between patients who successfully converted to sinus rhythm and those who remained in AF (Table 2).

**QT interval prolongation**
The QTc interval prolonged significantly in both groups, from 399±28 ms to 427±64 ms (p<0.001) in the ibutilide group and from 398±26 ms to 426±39 ms (p<0.001) in the propafenone plus ibutilide group. This increase was comparable between the two groups (p=0.99).

**Complications and safety profile**
One patient in the propafenone plus ibutilide group experienced an episode of sustained torsade de pointes, approximately 45 minutes after the onset of ibutilide infusion. The patient’s QTc interval increased from 407 ms to 520 ms after the infusion of the second dose of ibutilide, despite normal serum electrolyte levels. She was successfully cardioverted with a 300-Joule direct current monophasic shock, although a significant bradycardia ensued requiring external transthoracic pacing. No other significant complications were observed during the hospitalization period.

**DISCUSSION**
Pharmacological conversion of persistent AF is highly effective when initiated within 7 days after the onset of the arrhythmia. According to the current recommendations for pharmacological cardioversion of AF of more than 7 days duration, only dofetilide has a class I indication; amiodarone and ibutilide have a class IIa, while flecainide and propafenone have a class IIb indication. Previous reports have demonstrated low success rates for pharmacological cardioversion of persistent AF of over 7 days duration. As a result, the majority of patients with persistent AF of long duration are managed with electrical direct current cardioversion. This method is associated with high success rates and shorter monitoring time. However, the development of effective pharmacological treatments for cardioversion obviates the need for sedation or general anaesthesia and may represent a more cost-effective approach for such patients.

Propafenone is a class Ic antiarrhythmic agent that slows conduction in the atrial tissue by blocking the fast sodium current (INa). Its efficacy is well established, reaching up to 87% success rates when administered during the first hours after the initiation of the arrhythmia. In contrast, propafenone is much less effective in cardioversion of persistent AF, with reported success rates ranging between 4 and 9.3%. Of note, Kocihadakis et al. have reported that this rate can reach the level of 40% after 1 month of continuous oral administration.

Ibutilide, a class III antiarrhythmic agent, increases the action potential duration by blocking the rapid component of the delayed rectifier potassium current (IKr) and by enhancing the slow inward INa. It can cause significant QT interval
prolongation, leading to the development of torsade de pointes, albeit this complication is relative rare. Although ibutilide is more effective in conversion of atrial flutter (AFl), it is also considered one of the most potent agents for cardioversion of recent-onset AF, with success rates of up to 80%.

These rates decrease significantly, to the range of 30% to 40%, in patients with persistent atrial fibrillation lasting more than 4 days. Abi-Mansour et al. reported an efficacy rate of 28% in patients with AF duration of 3 hours to 90 days; further analysis, however, revealed mean arrhythmia duration of 13.6 days for patients successfully converted to sinus rhythm, compared to 35.4 days for those remained in atrial fibrillation.

Similarly, Eversole et al. included patients with arrhythmia duration ranging from 1 hour to 11 months and found a conversion rate of 17% in the subgroup of patients with arrhythmia duration greater than 96 hours. A recent study indicated that ibutilide successfully cardioverted 41.5% of patients with persistent AF lasting for 328±416 days (the series with the longest duration published so far), but these patients had sinus node disease with implanted dual chamber pacemakers. In accordance with these studies, we report a successful cardioversion rate for ibutilide alone of 41.1% in patients with persistent AF with a mean duration of 98±83 days.

The efficacy of ibutilide when combined with other antiarrhythmic drugs has not been adequately investigated. Ibutilide in patients with persistent AF, who were on long-term amiodarone treatment, was associated with 39% success rate within 30 minutes of administration. However, these agents belong to the same antiarrhythmic class, sharing common antiarrhythmic actions. In the present study, we evaluated the efficacy of ibutilide combined with a class Ic antiarrhythmic agent. We demonstrated that the concurrent administration of propafenone and ibutilide is superior to ibutilide alone. The success rate of 71.4% found in our study is the best result achieved by a pharmacological approach, and compares favourably with the 70-90% success rate of traditional external, direct-current cardioversion.

Very recently, two further studies investigated a similar pharmacological approach in patients with AF or AFl. In the first study, the effects of ibutilide were investigated in 56 patients with AF or AFl (mean duration: 64±44 days) who were pre-treated with propafenone. The authors reported a conversion efficacy of 62.5% within a 4-hour observation period after ibutilide administration; only 1 patient developed 2 asymptomatic, self-terminating episodes of torsade de pointes. Although only 7% of the total group had chronic AFl, the authors do not provide separate information on the success rates in the two subgroups, namely chronic AF and AFl. In the second report, 48 patients with persistent AF (mean duration 32±54 days) and 23 patients with AFl receiving propafenone or flecainide underwent pharmacological cardioversion with ibutilide. The success rate for patients with persistent AF was 47.9% with a trend towards higher conversion rates in those with arrhythmia duration of ≤7 days. Only 2 of the 71 patients with AF or AFl developed torsade de pointes.

To our knowledge, our study is the largest so far, investigating the role of the combination of a class Ic agent with ibutilide for cardioversion of persistent AF. In contrast with the two recent reports, our patient population was homogenous, including only patients with persistent AF of relative long duration. Moreover, three important methodological differences exist between our study and the two recently published reports. Firstly, our study directly compared ibutilide alone versus propafenone plus ibutilide. Secondly, in our study, propafenone was commenced at the beginning of the cardioversion process, whereas in the other two studies the patients were already pre-treated for a relatively long period. Since propafenone...
exerts rapid electrophysiological effects, pre-treatment does not appear to be justified.\textsuperscript{11,14} Lastly, pre-treatment with either propafenone or flecainide was previously used,\textsuperscript{24} although these drugs belong to the same antiarrhythmic class, significant differences in the acute success rates have been reported.\textsuperscript{8}

The two distinct peaks of AF conversion, observed in the propafenone plus ibutilide group, merit attention. The first peak, observed approximately 50 minutes after ibutilide administration, probably represents the peak pharmacologic action of ibutilide, while the second peak, around the 110\textsuperscript{th} minute after ibutilide administration, is most likely secondary to the synergistic action of propafenone and ibutilide. Given the pharmacokinetics of these two agents,\textsuperscript{11,13,14} one could speculate that even higher conversion rates can be achieved with the combined administration, if oral propafenone precedes the administration of intravenous ibutilide by approximately 60 minutes.

Our study, being free of the methodological limitations of the two previously published reports,\textsuperscript{23,24} provides more solid evidence for superior results with combined propafenone and ibutilide administration, compared to ibutilide alone. The risk for proarrhythmic or other side effects was comparable between the two regimens. Previous reports indicate an overall incidence of 4.3\% of torsade de pointes, including 1.7\% of the sustained form, in ibutilide-treated patients.\textsuperscript{13,18,20} The meticulous investigation for factors precipitating to proarrhythmia and the low percentage of patients with structural heart disease in our population may account for the low incidence of adverse reactions seen in our study.

**Study limitations**

We feel that our study adds to the current understanding of pharmacologic conversion of persistent AF. However, apart from the timing of propafenone administration, discussed earlier, a few potential limitations may be apparent. First, our study was not placebo-controlled and, therefore, the efficacy of each treatment arm, beyond that of placebo, cannot be directly assessed. Second, no data on long-term sinus rhythm maintenance are available. Lastly, the low incidence of proarrrhythmia may be due to the strict exclusion criteria applied in our study protocol; thus, extrapolation to patients with significant structural heart disease should be made with caution.

**Conclusion**

Our study indicates that, in selected patients with persistent AF of relatively long duration undergoing elective pharmacological cardioversion, propafenone can be safely added to ibutilide to increase sinus rhythm restoration rates. Further studies examining the optimal timing of propafenone administration prior to ibutilide infusion are needed. Moreover, the efficacy and safety of this regimen should be evaluated in other patient groups. Finally, comparison of this strategy with electrical cardioversion constitutes a subject for future research.
References

### Table 1 Baseline characteristics of the two groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ibutilide (n=51)</th>
<th>Propafenone plus Ibutilide (n=49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66(9)</td>
<td>65(11)</td>
<td>0.77</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>34 (66%)</td>
<td>32 (65%)</td>
<td>0.83</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>98(83)</td>
<td>99(100)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (52%)</td>
<td>28 (57%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (13%)</td>
<td>5 (10%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (19%)</td>
<td>8 (16%)</td>
<td>0.86</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>36(12)</td>
<td>43(17)</td>
<td>0.15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58(6)</td>
<td>59(10)</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>92(13)</td>
<td>95(11)</td>
<td>0.62</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>399(28)</td>
<td>398(26)</td>
<td>0.90</td>
</tr>
<tr>
<td>Drugs for rate control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>38 (74%)</td>
<td>37 (75%)</td>
<td>0.90</td>
</tr>
<tr>
<td>β-blockers</td>
<td>22 (43%)</td>
<td>21 (42%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>7 (13%)</td>
<td>5 (10%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Values are expressed as mean(SD) or as n (%).
AF, atrial fibrillation; LA, left atrial; LVEF, left ventricular ejection fraction; bpm, beats per minute; ms, milliseconds.

### Table 2 Predictors of conversion success in the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conversion (n=56)</th>
<th>No Conversion (n=44)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65(11)</td>
<td>64(9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>36 (64%)</td>
<td>30 (68%)</td>
<td>0.84</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>86(76)</td>
<td>115(107)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (51%)</td>
<td>26 (59%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (12%)</td>
<td>5 (11%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (14%)</td>
<td>10 (22%)</td>
<td>0.40</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>37(6)</td>
<td>42(8)</td>
<td>0.15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59(9)</td>
<td>57(8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Baseline heart rate (bpm)</td>
<td>96(12)</td>
<td>90(15)</td>
<td>0.41</td>
</tr>
<tr>
<td>Baseline QTc interval (ms)</td>
<td>400(27)</td>
<td>395(26)</td>
<td>0.67</td>
</tr>
<tr>
<td>QTc interval increase (ms)</td>
<td>22(21)</td>
<td>42(57)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Values are expressed as mean(SD) or as n (%).
AF, atrial fibrillation; LA, left atrial; LVEF, left ventricular ejection fraction; bpm, beats per minute; ms, milliseconds.
Figure legend

Figure 1 Timing of conversion to sinus rhythm (expressed in minutes after the onset of ibutilide administration) in patients who received ibutilide (open bars) or propafenone plus ibutilide (solid bars).
ibutilide

propafenone plus ibutilide