Abstract. – Background: Atrial fibrillation is the most frequent cardiac rhythm disturbance, with prevalence increasing with age. This disease is a major risk factor for ischaemic stroke. The costs resulting from atrial fibrillation are really impressive. Pharmacological agents are the first line therapy for the management of atrial fibrillation. Antiarrhythmic drugs are used to terminate arrhythmias, as acute treatment for conversion of recent onset atrial fibrillation, and to maintain sinus rhythm, as chronic therapy for prevention of atrial fibrillation recurrences. Among antiarrhythmic agents, drugs that inhibit early sodium current (as propafenone) are proven effective in atrial fibrillation. In this review, the most relevant data on propafenone are provided.

Discussion: The development of a sustained-release formulation of propafenone allowed to reduce the wide fluctuations in plasma levels observed with the immediate release preparation, improving compliance and adherence to therapy, by simplifying the dosing regimen from 3 to 2 daily doses. Propafenone resulted an effective measure as acute treatment for conversion of recent onset atrial fibrillation, and to maintain sinus rhythm, as chronic therapy for prevention of atrial fibrillation recurrences. In several clinical studies, strong increases of arrhythmia-free periods as well as marked increases in time to recurrence of symptomatic atrial fibrillation, such as paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation were observed. In particular, well-designed clinical studies demonstrated in large patient populations the efficacy of propafenone at several doses. At the suggested doses propafenone is usually well tolerated.

Conclusion: The risk of increased occurrence of regular supraventricular arrhythmia or paroxysmal supraventricular tachycardia has been overestimated for propafenone, because this adverse event was seen in all treatment groups, including placebo, with the same (and low) frequency.

Key Words: Atrial fibrillation (AF), Acute onset AF, Prevention of AF recurrences, Antiarrhythmic drugs, Propafenone.
The clinical relevance and the high costs of atrial fibrillation account for the need of effective drug treatment.6
As for the management of atrial fibrillation, the main therapeutic strategies include:

- Rate control;
- Termination of arrhythmia;
- Prevention of recurrences;
- Prevention of thromboembolic events.11

Pharmacological agents are the first line therapy for rhythm management in atrial fibrillation.1,6
Antiarrhythmic drugs are used to terminate arrhythmias and maintain sinus rhythm.6,11
Efficacy and safety profiles are extremely important issues in the choice of an antiarrhythmic agent, but also the dosing convenience (allowing high patient compliance) should be taken in due account.11 According to current guidelines, it is suggested to select an antiarrhythmic drug considering some main factors, in order to identify the best therapeutic strategy:

- Symptoms presentation;
- Atrial fibrillation characteristics;
- Presence of cardiovascular diseases;
- Patient age and medical conditions;
- Treatment goals.6

Among antiarrhythmic agents, drugs that inhibit early sodium current (as propafenone and flecainide) are proven effective in atrial fibrillation.12,13 The most widely used antiarrhythmic drugs are listed in Table I.

According to most recent guidelines and updated meta-analyses, as well as to the Author’s personal caseload, it is possible to anticipate some general considerations on the pharmacological approach to atrial fibrillation.

As for other chronic treatments, also for antiarrhythmic drugs the choice of the proper therapy should balance at the best efficacy and safety.

The group of antiarrhythmic drugs includes different molecules showing each a typical profile of efficacy, safety and convenience. Table II reports some observations on main antiarrhythmic agents.6,14-16.

We can state, therefore, that propafenone, thanks to its clinical efficacy associated to a good safety (in particular to a reduced risk of proarrhythmic effect), can represent an important measure in the management of atrial fibrillation patients not showing cardiac structural alterations. In addition, this drug, due to the availability of vials for intravenous use, immediate release tablets, and sustained release capsules, allows to develop various treatment schedules and to adapt the therapy according to different needs.

**Focus on Propafenone**

Propafenone is a powerful class antiarrhythmic agent, with demonstrated effectiveness against a variety of cardiac arrhythmias.12-14 This agent shows a marked inhibitory effect on the sodium channel and some beta-blocking activity.5,14-17

The original formulation of oral propafenone immediate release was rapidly absorbed by gastrointestinal tract and metabolized by liver, needing a 3 times daily administration.13,17
Propafenone 150-300 mg tid is associated to a half-life of 5-7 hours, wide fluctuations in peak-trough plasma concentrations, and a marked interindividual variability.17,19 To solve these problems, a sustained-release preparation (SR) has been subsequently developed, improving compliance, efficacy, and safety.5,14-17,18 Thank to its prolonged half-life (12 hours), this latter propafenone formulation allows a twice daily administration, with better compliance and adherence to therapy.12,13,17,18 In addition, based on the official data on propafenone pharmacokinetics derived from SPC, we underline the importance of the curves reported in Figure 1.

Propafenone undergoes extensive hepatic metabolism: the main products of oxidative metabolism are 5-hydroxy-propafenone and hydroxy-methoxy-propafenone.5,17 In particular, 5-hydroxy-propafenone shows a pharmacodynamic

### Table I. Main antiarrhythmics drugs.

<table>
<thead>
<tr>
<th>Class</th>
<th>Sodium channel blockers</th>
<th>Potassium channel blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ia</td>
<td>Disopyramide, procainamide, quinidine</td>
<td>Class III</td>
</tr>
<tr>
<td>Class Ic</td>
<td>Flecainide, propafenone</td>
<td></td>
</tr>
</tbody>
</table>

*USA only. (Adapted from 6).
Propafenone resulted an effective measure as acute treatment, for conversion of recent onset atrial fibrillation and to maintain sinus rhythm, as chronic therapy, for prevention of atrial fibrillation recurrences.

As for pharmacodynamics, the principal activities of propafenone are arrhythmia suppression, intracardiac conduction and beta-adrenergic blockade.

Some drugs, relatively more recent (as propafenone, flecainide, procainamide and sotalol), are at least as effective as some less recent agents, as quinidine and disopyramide.

At the same time, propafenone, flecainide, procainamide and sotalol are better tolerated than quinidine and disopyramide.

Among the most active agents, the proarrhythmic effect is less frequent with propafenone and amiodarone.

As for proarrhythmic effect, no statistically significant differences were found when comparing propafenone and amiodarone with placebo.

In particular, in the Ic class propafenone shows a lower frequency of proarrhythmic effects as compared with flecainide.

Propafenone is a powerful Ic antiarrhythmic agent, widely used for sinus rhythm restoration and maintenance.

In meta- and mixed-analyses, sotalol and propafenone were evaluated as for the safety profile in the widest patients populations (more than 1,000 patients), as compared with amiodarone (n = 437) or flecainide (n = 114).

Table II. Selected data on main antiarrhythmics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma concentration (µM)</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>propafenone</td>
<td>2.5</td>
<td>72</td>
</tr>
<tr>
<td>propafenone</td>
<td>1.5</td>
<td>120</td>
</tr>
<tr>
<td>propafenone</td>
<td>0.5</td>
<td>172</td>
</tr>
<tr>
<td>propafenone</td>
<td>2.0</td>
<td>224</td>
</tr>
</tbody>
</table>

(Adapted from 6, 14, 15, 16).

Profile similar to the parent drug, thus contributing to the therapeutic efficacy.

As for pharmacodynamics, the principal activities of propafenone are arrhythmia suppression, intracardiac conduction and beta-adrenergic blockade.

Propafenone Clinical Efficacy

Propafenone resulted an effective measure as acute treatment, for conversion of recent onset atrial fibrillation and to maintain sinus rhythm, as chronic therapy, for prevention of atrial fibrillation recurrences.

Figure 1. Propafenone plasma levels following repeated oral doses of slow-release formulation (325 and 425 mg) and immediate-release (150 and 300 mg).
Acute Treatment: Conversion to Sinus Rhythm

The objectives of acute treatment of atrial fibrillation are:

• To reduce atrial fibrillation duration;
• To avoid the need for anticoagulants, required for atrial fibrillation that lasts more than 48 h;
• To reduce hospital stay.

The acute treatment is usually required in atrial fibrillation of recent onset, such as an arrhythmia of <48 to 72 hours duration.

Propafenone as intravenous formulation resulted effective in converting atrial fibrillation to sinus rhythm in several studies. The dosing scheme was an intravenous single bolus (2 mg/kg) or an intravenous bolus (2 mg/kg) followed by an intravenous infusion.

After an intravenous bolus, the efficacy rates were of 51% to 88%, increasing up to 91% with intravenous infusion.

When considering efficacy, also the time of sinus rhythm restoration must be considered: in a meta-analysis of clinical trials, the proportions of patients attaining sinus rhythm with intravenous propafenone were: at 1 hour 57%; at 2 hours 66%; at 4 hours 51%; at 8 hours 69%.

The use of propafenone as oral loading doses (450 mg to 600 mg) appears a useful alternative to the intravenous route, producing therapeutic plasma levels of propafenone and its active metabolite, 5-hydroxy-propafenone.

At doses of 450 mg to 600 mg, propafenone resulted associated with a success rate between 66% and 76% at 8-12 hours from administration.

The efficacy of oral loading with propafenone in converting atrial fibrillation to sinus rhythm has been demonstrated versus placebo and active treatments in several studies. A comparison of different drug protocols, including intravenous and oral loading propafenone, intravenous amiodarone, oral flecainide, and placebo, with assessments made at different times, showed that:

• At ≤ 1 hour, only intravenous propafenone was effective;
• At ≤ 3 hours, all treatments were effective, except amiodarone;
• At ≤ 8 hours, all comparisons vs placebo were statistically significant.

Figure 2 shows the cumulative results of 7 comparative studies versus placebo in 934 patients.

A comparison of different drug protocols, including intravenous and oral loading propafenone, intravenous amiodarone, oral flecainide, and placebo, with assessments made at different times, showed that:

• Propafenone 300 mg bolus per os, followed by further 300 mg after 8 hours, if the sinus rhythm was not reached (n = 43);
• 1 mg digoxin iv, followed by oral quinidine loading dose: 400 mg per os and additional 200 mg every 2 hours (n = 38)\textsuperscript{28}.

The length of treatment was not exceeding 24 hours\textsuperscript{28}.

At 8 hours propafenone was associated with a success rate of 83.3\% versus 53\% of quinidine ($p = 0.01$)\textsuperscript{28}.

Also the time to restore sinus rhythm was significantly shorter with propafenone than quinidine: 165 minutes versus 360 minutes ($p = 0.05$)\textsuperscript{28}.

Figure 4 shows the number of patients with atrial fibrillation in this study\textsuperscript{28}.

Naccarelli et al\textsuperscript{11} carried out an overview of clinical trials on efficacy of antiarrhythmic drugs in converting and maintaining sinus rhythm. In this analysis the best pharmacological strategies for acute control of atrial fibrillation were evaluated.

Comparative efficacy of oral quinidine, sotalol, oral bolus propafenone, and intravenous amiodarone versus and placebo, estimated as conversion rates for recent-onset atrial fibrillation, is reported in Figure 5.

According to the data shown in Figure 5, in atrial fibrillation\textsuperscript{11} of recent onset the highest efficacy was observed for propafenone 300 mg bid.

In the management of paroxysmal atrial fibrillation, propafenone and flecainide resulted the most effective agents in order to obtain the conversion to sinus rhythm\textsuperscript{29}. Some differences were observed, however, when considering the control exerted by these two drugs on heart rate in patients who failed cardioversion\textsuperscript{29}. In fact, flecainide induced a reduction of heart rate from 9\% to 13\%, a result comparable to that observed with placebo, while propafenone was associated with a reduction of heart rate from 15\% to 31\%. Very likely, this result is related with the beta-blocking properties typical of propafenone\textsuperscript{29}.

The marked activity of propafenone, as acute treatment by oral route, and the quick onset of therapeutic action led to the “pill in the pocket” strategy, implying the drug is taken per os shortly after a symptomatic recurrence appears: this approach was described by Alboni et al\textsuperscript{30} in 2004. Obviously, the “pill in the pocket” approach, which can be performed out of hospital, should be adopted only in selected patients, who already experienced the safety of such a treatment during a hospital stay.

**Chronic treatment: Sinus Rhythm Maintenance and Prevention of Atrial Fibrillation Recurrences**

Several benefits are associated to sinus rhythm maintenance:

• Prevention of atrial electrical remodelling, slowing disease progression;
• Improvement of hemodynamics by restoring atrial transport function;
• Enhancement of exercise capacity;
• Relief of symptoms, with quality of life improvement;
• Reduction of thromboembolic events.

![Figure 4. % of patients with atrial fibrillation who received propafenone or quinidine per os. (Adapted from 28).](image-url)
According to International Guidelines, in order to prevent recurrences of atrial fibrillation, it is often suggested a pharmacological treatment that can be performed by antiarrhythmic agents, able to maintain sinus rhythm\textsuperscript{36}. Among antiarrhythmic agents, propafenone resulted an effective measure in several clinical studies, allowing strong increases of arrhythmia-free periods as well as marked increases in time to recurrence of symptomatic atrial fibrillation: thus propafenone is of value in the prophylaxis of both paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation\textsuperscript{11-13,31-35}.

The efficacy of immediate release propafenone formulation was already demonstrated as soon as the drug became available in Europe and USA in the 80’s\textsuperscript{12}.

ERAFT and his sister trial from North America RAFT have been designed to definitely assess the effectiveness of the SR (Sustained Release) formulation in the prophylaxis of atrial fibrillation recurrence\textsuperscript{12,13}. Therefore, for the most recent SR propafenone formulation, these two large and well-conducted studies are described\textsuperscript{12,13}.

The ERAFT (the European Rythmol/Rytmo-norm Atrial Fibrillation Trial) was a multicenter prospective, randomized double-blind, placebo-controlled parallel group study, that compared propafenone 325 mg bid, propafenone 425 mg bid, and placebo in a large patient population\textsuperscript{12}. The objective of the trial was to demonstrate the drug efficacy in the prevention of recurrences of symptomatic paroxysmal atrial fibrillation\textsuperscript{12}. The primary efficacy analysis was based on the arrhythmia-free period form 5\textsuperscript{th} day from randomization to first recurrence of symptoms of atrial fibrillation (primary endpoint)\textsuperscript{12}. A total of 293 patients were randomized to the 3 treatment arms:

- 111 to propafenone 325 mg bid;
- 89 to propafenone 425 mg bid;
- 93 to placebo bid\textsuperscript{12}.

The results of the trial showed, as primary efficacy analysis, that the most frequent diagnosis of symptomatic arrhythmia observed after 5 days was atrial fibrillation\textsuperscript{12}.

It has been evidenced a significant increase in the arrhythmia-free period from 5\textsuperscript{th} day from randomization to first recurrence in the 2 propafenone groups compared with placebo: 325 mg bid $p = 0.004$ and 425 mg bid $p = 0.003$ (Table III)\textsuperscript{12}.

The median duration of arrhythmia-free period was 9 days for the placebo group, 35 days for the propafenone SR 325 mg bid group, and 44 days for the propafenone SR 425 mg bid group ($p < 0.001$ in favour of propafenone in both comparisons versus placebo)\textsuperscript{12}. These differences resulted even greater wen adopting the per-protocol analysis, such as when the analysis was restricted to patients adherent to study protocol, instead of performing the full data analysis (Figure 6)\textsuperscript{12}. 

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Antiarrhythmic conversion of recent-onset atrial fibrillation: comparative efficacy of different pharmacological agents. (Adapted from 9).}
\end{figure}
In conclusion, the ERAFT study demonstrated in a large patient population the efficacy of propafenone SR formulation. The results of this trial, using propafenone SR 2 times daily, are consistent with the results of other studies adopting the immediate release formulation 3 times daily. In particular, the PSVT (UK Propafenone Paroxysmal Supraventricular Tachycardia) study, conducted on patients with two or more recurrences of atrial fibrillation, compared propafenone 300 mg bid versus placebo, followed by 300 mg tid versus placebo in a crossover design. The mean time to arrhythmia was 11 days in the placebo group vs > 98 days in the propafenone bid group.

The RAFT (Rythmol Atrial Fibrillation Trial) was a randomized double-blind, placebo-controlled study, carried out in USA, that compared propafenone 225 mg bid, propafenone 325 mg bid, propafenone 425 mg bid, and placebo in patients not previously exposed to this agent. The objective of the trial was to demonstrate the propafenone efficacy in reducing symptomatic arrhythmia recurrences in patients with atrial fibrillation.

The primary outcome event was the first of electrocardiograms coded as atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia. Patients completed the study if they had an outcome event or if they finished the 39 weeks of follow-up.

A total of 523 patients were randomized to the 4 treatment arms:

- 126 to propafenone 225 mg bid;
- 135 to propafenone 325 mg bid;
- 136 to propafenone 425 mg bid;
- 126 to placebo bid.

The analysis of all patients showed a median time to the occurrence of a primary outcome event of 41 days in placebo group, of 112 days in the propafenone 225 mg group, 291 days in the propafenone 325 mg group, and >300 days in the propafenone 425 mg bid group (Table IV).

In the primary efficacy analysis, statistically significant differences between placebo and propafenone were recorded:

- \( p < 0.001 \) for propafenone 425 mg;
- \( p < 0.001 \) for propafenone 325 mg;
- \( p = 0.014 \) for propafenone 225 mg.

These data are shown in Figure 7.

The survey of Naccarelli at al, already quoted for acute treatment of atrial fibrillation, included also an evaluation of the efficacy of antiarrhythmic drugs in the recurrence prevention. According to the results of 6 main studies, comparing oral propafenone, flecainide, sotalol, and quinidine, it can be evidenced that propafenone was significantly more effective.
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than sotalol and quinidine (p < 0.01 and p < 0.05, respectively), while propafenone and flecainide were equally effective.

Safety

In the most clinical studies propafenone resulted well tolerated, with only minor side-effects11,12,13,17,34-36.

In the RAFT study, for instance, adverse events were generally comparable among the placebo twice daily group and the two propafenone groups, 225 and 325 mg bid12. When comparing the safety profiles of propafenone and flecainide, it can be observed that the frequency of side effects not requiring treatment withdrawal was significantly higher with flecainide: 48% versus 8% of propafenone (p < 0.01)29.

Interestingly, in the RAFT study, propafenone did not result associated with an increased occur-

Figure 6. Tachyarrhythmia-free period (absence of symptomatic atrial fibrillation or atrial flutter) from day 5 of randomization. (Adapted from 10).
Figure 7. RAFT Study: efficacy analysis in all randomized patients. Time to first symptomatic arrhythmia recurrence. (Adapted from 11).

Table IV. Results of RAFT study: efficacy of propafenone 225, 325, and 425 mg versus placebo.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>225 mg</th>
<th>325 mg</th>
<th>425 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients</td>
<td>126</td>
<td>135</td>
<td>136</td>
<td>126</td>
</tr>
<tr>
<td>Patients with symptomatic outcome arrhythmia documented by electrocardiogram</td>
<td>66 (52%)</td>
<td>56 (42%)</td>
<td>41 (30%)</td>
<td>87 (69%)</td>
</tr>
<tr>
<td>Time to outcome arrhythmia Kaplan-Meier, median (d)</td>
<td>112</td>
<td>291</td>
<td>300</td>
<td>41</td>
</tr>
<tr>
<td>Range (d)</td>
<td>0-285</td>
<td>0-293</td>
<td>0-300</td>
<td>0-289</td>
</tr>
<tr>
<td>Log-rank p value vs placebo</td>
<td>0.014</td>
<td>0.001</td>
<td>0.001</td>
<td>–</td>
</tr>
<tr>
<td>Hazard ratio (propafenone: placebo)</td>
<td>0.672</td>
<td>0.434</td>
<td>0.353</td>
<td>–</td>
</tr>
<tr>
<td>95% CI for hazard ratio</td>
<td>(0.488-0.927)</td>
<td>(0.309-0.609)</td>
<td>(0.243-0.513)</td>
<td>–</td>
</tr>
<tr>
<td>Patients in sinus rhythm after loading period</td>
<td>124</td>
<td>132</td>
<td>131</td>
<td>124</td>
</tr>
<tr>
<td>Patients with symptomatic outcome arrhythmia documented by electrocardiogram</td>
<td>60 (48.4%)</td>
<td>54 (40.9%)</td>
<td>36 (27.5%)</td>
<td>84 (67.7%)</td>
</tr>
<tr>
<td>Time to outcome arrhythmia Kaplan-Meier, median (d)</td>
<td>149</td>
<td>287</td>
<td>296</td>
<td>39</td>
</tr>
<tr>
<td>Range (d)</td>
<td>0-281</td>
<td>0-289</td>
<td>0-296</td>
<td>0-285</td>
</tr>
<tr>
<td>Log-rank p value vs placebo</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>–</td>
</tr>
<tr>
<td>Hazard ratio (propafenone: placebo)</td>
<td>0.604</td>
<td>0.438</td>
<td>0.319</td>
<td>–</td>
</tr>
<tr>
<td>95% CI for hazard ratio</td>
<td>(0.433-0.842)</td>
<td>(0.310-0.619)</td>
<td>(0.216-0.473)</td>
<td>–</td>
</tr>
</tbody>
</table>

CI = confidence intervals. (Adapted from 11).
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The increase in the occurrence of regular supraventricular arrhythmia with ECG, typical for atrial flutter or paroxysmal supraventricular tachycardia, was a supposed effect widely reported when the class Ic antiarrhythmic drugs was introduced on the market13. The Authors of RAFT report suggest that this problem has been possibly overestimated for propafenone, as it was seen in all treatment groups, including placebo, with the same and low frequency13.

These data were recently confirmed by the Cochrane Collaborative Group, who carried out a systematic review on the efficacy and safety of antiarrhythmic agents in maintaining the sinus rhythm after cardioversion of atrial fibrillation16. The analysis of available studies evidenced that among these drugs only propafenone and amiodarone did not differ from placebo as for proarrhythmic effect16. In particular, when comparing propafenone and flecainide, a marked difference in Odd’s Ratios was seen, as reported in Table V16.

The available evidence allows concluding that propafenone can be an effective therapeutic measure in the management of atrial fibrillation, in both approaches: the acute treatment, for conversion of sinus rhythm, and the chronic treatment, for maintenance and prevention of atrial fibrillation recurrences, with a good safety profile.

As for administration schemes (described in the data sheet for prescriber information)37, propafenone allows proper therapeutic schedules for acute treatment through two formulations, solution for intravenous use and immediate-release tablets, while the sustained-release capsules represent the ideal bid presentation for maintaining sinus rhythm, with a favourable impact on compliance and adherence of patients to the therapy.

### References


4) **Anter E, Collans DJ, Wise DG.** Pharmacological and electrical conversion of atrial fibrillation sinus rhythm is worth to effort. Circulation 2009; 120: 1436-1443.


### Table V

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Nr of studies</th>
<th>Nr of patients</th>
<th>Effect size° (95% IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>3</td>
<td>149</td>
<td>5.97 (1.67-21.34)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>5</td>
<td>1098</td>
<td>1.52 (0.33-7.02)</td>
</tr>
</tbody>
</table>

(Adapted from 28).


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37) Propafenone Prescriber Information. Update by Health Authorities in 2010.