Restoring sinus rhythm (SR) in patients with atrial fibrillation (AF) relies on three main objectives: 1) to find and treat a predisposing factor; 2) to prevent thromboembolic complications and 3) to cardiovert as soon as possible to avoid atrial remodeling and obtain SR more easily [1-2]. For this last purpose, pharmacological or electrical cardioversion may be used. However, electrical cardioversion requires a short general anesthesia and pharmacological cardioversion requires antiarrhythmic drugs (AAD) with potential short-term side effects. Hospitalization is therefore recommended to monitor patients in both cases. In 2003, Capucci et al. reported a first series of 212 consecutive patients who achieved safe cardioversion in response to oral propafenone under close supervision in the hospital. AF recurred in 65 of these patients who underwent a new in-hospital oral propafenone treatment without significant side effects [3]. These results suggested to safely use the pill-in-the-pocket approach in selected patients. In 2005, Alboni et al. reported a prospective study evaluating a strategy of rhythm control by a self-administration of AAD (flecainide or propafenone) in selected patients with paroxysmal AF [4]. Using this strategy shortly after the onset of arrhythmia, this study showed decreased hospital admissions, decreased management costs and improved quality of life. These encouraging results led to the inclusion of the pill-in-the-pocket strategy in selected patients in recent American and European guidelines [1-2].

I. THE CHOICE OF ANTIARYRTHMIC DRUGS FOR THE PILL-IN-THE-POCKET STRATEGY

Before any attempt to reduce AF, a predisposing factor such as chronic or acute alcohol intoxication (Holiday heart syndrome) should be assessed. In this case, alcohol elimination will often lead to spontaneous recovery of SR and no AAD will be needed if arrhythmia is well tolerated. Hyperthyroidism or hypokalaemia require correction before considering the use of AAD. Other predisposing factors will require concomitant treatment (fever, pneumonia, pericarditis, etc.). Prevention of AF recurrence will also rely on treating the causal heart disease or sleep apnea syndrome.

Moreover, it is important to note that AF can stop spontaneously in nearly 50% of cases during the first 24 hours especially in the absence of underlying heart disease [5]. If AF is well tolerated, effective anticoagulation alone may be decided in this case while waiting for spontaneous recovery of SR in order to prevent AAD side effects.

Three of the currently available AADs (flecainide, propafenone and amiodarone) are commonly used to reduce AF. These agents have demonstrated their efficacy either after oral or intravenous administration [6-12]. Quinidine is less used because of frequent side effects and lower efficacy [13], Sotalol is not more efficient than placebo [14]. Dofetilide is not recommended for a pill-in-the-pocket strategy [1].

The choice of AAD depends on the existence of an underlying heart disease and the duration of AF (Fig. 1). In case of a structural heart disease only amiodarone will be indicated in the absence of hyperthyroidism. If AF lasted less than 48 hours, and in the absence of heart disease, flecainide and propafenone are considered more effective than amiodarone. This latter AAD is preferred in case of persistent AF [2]. Flecainide, propafenone and

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FIGURE 1

Adapted decision algorithm for cardioversion in recent-onset paroxysmal AF from 2010 European Guidelines (www.escardio.org/guidelines).
Amiodarone may be used orally or intravenously for cardioversion (Table I).

In the particular case of AF occurring in a patient with an accessory pathway with a rapid ventricular response, the risk is the occurrence of ventricular fibrillation (VF). In this case, cardioversion will be performed in hospital using either flecainide IV or electrical cardioversion.

II. Efficacy of Currently Available Antiarrhythmic Drugs

A. Flecainide

For a rapid cardioversion, intravenous administration is preferable to the oral route especially in hospital [8-9]. When the oral route is used as in the pill-in-the-pocket strategy, cardioversion is obtained mainly in 60% of the cases 2 to 4 hours later and in 80% of the cases 8 hours later. The recommended dosage is 4 mg/kg without exceeding 300 mg. Flecainide is contraindicated in case of an underlying structural heart disease or in case of a Brugada syndrome. Side effects are mainly the occurrence of a fall in blood pressure or atrial flutter with rapid conduction 1/1 to the ventricles. The width of the QRS must be monitored as an increase > 30% calls for the discontinuation of the medication.

B. Propafenone

The efficacy of propafenone is comparable to that of flecainide: 60 to 80% of cardioversions are obtained on recent AF 2 to 6 hours after oral administration of 600 mg [10-11]. Side effects are similar to those of flecainide. Because of the properties of propafenone, it can also induce a moderate bradycardia.

C. Amiodarone

In case of structural heart disease, flecainide and propafenone are not recommended and amiodarone can be indicated. Amiodarone is less efficient than flecainide or propafenone during the first eight hours after administration. However, after 24 hours the difference disappears [14-15]. Moreover, when AF lasts more than 48 hours, amiodarone is more effective than class IC AADs. An oral loading dose of 30 mg/kg is needed. Besides hypotension or bradycardia, amiodarone can cause QT prolongation and rarely torsades de pointes requiring ECG monitoring. According to the longer delay in restoring SR, amiodarone does not seem to be accurate for a pill-in-the-pocket strategy. Moreover, no study evaluated this medication in out-hospital treatment strategy.

Recently, ranolazine, an anti-anginal agent that inhibits normal and abnormal late Na+ channel current in the ventricle and peak Na+ channel current in the atrium, has been shown to have a beneficial effect as an antiarrhythmic agent in AF [16-17]. A small non-randomized study showed also promising results in conversion of AF using a pill-in-the-pocket approach [18]. However, further studies are needed to confirm these results before using it in this indication.

Finally, when a pill-in-the-pocket strategy is decided, it seems more accurate to investigate in-hospital safety of oral administration rather than intravenous administration of AAD. In a study by Alboni et al., safety of intravenous cardioversion of AF of recent onset using flecainide or propafenone did not reflect safety of out-hospital use of these AADs [19]. In this study, 122 patients were successfully treated in hospital, within two hours and without major adverse effects, with intravenous flecainide or propafenone. They were discharged on pill-in-the-pocket treatment.

During a mean follow-up of 11 months, 79 patients used the treatment in 213 arrhythmic episodes. Success rate was 94%. However, the study was prematurely terminated because of the high incidence of major adverse events (4 patients, 5%) during the first self-treatment: one syncope, two presyncopes and one sinus arrest.

III. Side Effects and Selection of Patients

The pill-in-the-pocket strategy is based on the self-administration on prescription by the patient of a single dose of oral AAD: flecainide 200 to 300 mg or propafenone 600 mg are up to now the only AADs that were studied in this indication. The aim of this approach is to limit the duration of patient symptoms and to avoid hospitalizations and resulting costs. However, both flecainide and propafenone have potential side effects (sinus or atrioventricular node dysfunction, bundle branch block, induced atrial flutter, Brugada syndrome). Therefore, it is suggested, after respecting contraindications, to verify their safety during a hospitalization for a first attempt to restore SR.

On the other hand, to avoid overuse of these AADs, this

<table>
<thead>
<tr>
<th>Administration</th>
<th>Flecainide</th>
<th>Propafenone</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenously</td>
<td>2 mg/Kg over 10 minutes</td>
<td>2 mg/Kg over 10 minutes</td>
<td>5 mg/Kg over one hour &amp; follow-up dose : 50 mg/h</td>
</tr>
<tr>
<td>Orally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Pill-in-the-pocket</td>
<td>200 - 300 mg</td>
<td>450 - 600 mg</td>
<td>30 mg/Kg</td>
</tr>
<tr>
<td>&gt; Loading dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE I

Recommended Intravenous or Oral Doses of Flecainide, Propafenone and Amiodarone for Rapid Atrial Fibrillation Conversion
strategy should be limited to patients with infrequent symptomatic episodes of paroxysmal atrial fibrillation and who will be able to understand its modalities. A first study using propafenone by Capucci et al. showed no proarhythmic events [3]. They concluded that this therapeutic approach might be used in patients with demonstrated reproducibility of the therapy. However, they suggested using it only in patients who could correctly self-diagnose the symptoms of recurrent AF and who could self-manage the therapy including tablet intake and bed rest until sinus rhythm conversion.

Later, Alboni et al. evaluated this approach in 2004 in a randomized study that showed a significant decrease in hospitalizations with efficiency in 94% of cases [4]. In this study, treatment was used with a mean of 36 minutes after the onset of symptoms that disappeared with a mean of 2 hours later. Side effects occurred in 7% of cases. A case of fast conducting atrial flutter has been reported. Therefore, in recent international recommendations, this approach is considered acceptable and safe in selected subjects with paroxysmal infrequent AF. However, it is not recommended in patients with impaired left ventricular function or ischemic heart disease. The potential occurrence of fast conducting atrial flutter leads to the prescription of a short acting β-blocker or nondihydropyridine calcium channel antagonist at least 30 min before the administration of type IC AAD [20]. However, bradycardia may result from this association that requires to be careful in the choice of AAD and other medications [21]. Moreover, sudden death related to idiopathic ventricular fibrillation may occur in patients with the Brugada syndrome following administration of class I antiarrhythmic drugs even in patients with structurally normal hearts. Hidden ECG Brugada pattern revealed after oral propafenone administration in the setting of pharmaceutical atrial fibrillation cardioversion have been reported [22].

Because of these potential adverse events, an initial conversion is recommended in hospital before a patient is declared fit for outpatient pill-in-the-pocket use of flecainide or propafenone for conversion of paroxysmal AF [1].

IV. CONCERNS ABOUT ANTICOAGULATION

The aim of the pill-in-the-pocket approach is only to treat symptoms related to infrequent paroxysmal AF of recent onset and to avoid hospitalization. In the randomized study by Alboni et al. patients used the AAD meanly 36 minutes only after symptoms onset [4]. Moreover, patients had no underlying heart disease and their mean age was under 75 years. Therefore, thromboembolic risk was low in these patients. In patients with a higher thromboembolic risk, anticoagulants should be part of the treatment.

In conclusion, the choice of the pill-in-the-pocket strategy for AF cardioversion is safe when used appropriately. It should be limited to selected patients without underlying heart disease and after safety assessment during a hospitalization for a first cardioversion attempt.

REFERENCES