The ‘pill-in-the-pocket’ strategy for paroxysmal atrial fibrillation

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ARRHYTHMIAS UPDATE, THESSALONIKI 2017
‘Pill in the pocket’ cardioversion of atrial fibrillation

- Flecainide
- Propafenone
How Class IC AADs convert AF to SR?

- Class IC AADs inhibit the fast-inward sodium channels.

- Class IC AADs terminate AF by causing a tachycardia-dependent increase in atrial effective refractory period and wavelength, reducing the number of re-entrant circuits, so that the arrhythmia can no longer sustain itself.
Electrophysiological properties of class IC AADs

- Class IC AADs produce a dose-dependent decrease in intracardiac conduction, but their effects on intra-atrial and AV nodal conduction are less pronounced than those on His – Purkinje conduction and ventricular activation.

- They prolong the PR (17 – 29%) and QT (4 – 11%) intervals and the QRS complex (11 – 27%). Most of the QT prolongation is due to a widening of the QRS complex, so that the JT interval and the rate-corrected QT interval (QTc) remain unchanged or slightly increase (3–8%).

- Class IC also prolongs atrial, AV nodal and ventricular refractoriness, but its effects on refractoriness are less pronounced than its effects on intracardiac conduction.

- Flecainide does not affect sinus rate, although bradycardia and tachycardia have been occasionally reported. Flecainide increases the corrected sinus node recovery time and the sinoatrial (SA) conduction time in patients with sinus node dysfunction.
Outpatient Treatment of Recent-Onset Atrial Fibrillation with the “Pill-in-the-Pocket” Approach

- 268 pts with mild heart disease or none; Of the 268 patients who were treated, 58 were not given out-of-hospital treatment for the following reasons; Four patients were lost from follow-up.

- The dose of flecainide was 300 mg if the patient weighed 70 kg or more and was 200 mg otherwise; the dose of propafenone was 600 mg if the patient weighed 70 kg or more and was 450 mg otherwise.

- In-hospital drug-induced side effects were seen in 5% of patients, including transient hypotension, transient atrial flutter, and slightly symptomatic bradycardia.

- During a mean follow-up of 15±5 months, 165 out of 206 patients (79 percent) had a total of 618 episodes of arrhythmia; of those episodes, 569 (92 percent) of which were treated with either flecainide (in 64 patients) or propafenone (in 101 patients).

- Treatment was successful in 534 episodes (94 percent); the time to resolution of symptoms was 113±84 minutes.

- Adverse effects were reported during one or more arrhythmic episodes by 12 patients (7 percent), including atrial flutter at a rapid ventricular rate in 1 patient and non-cardiac side effects in 11 patients.
Conversion of Recent-Onset Atrial Fibrillation: the ‘single oral dose’
Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF study

- Pharmacologic cardioversion was enhanced by class IC antiarrhythmic drugs; conversion rate on amiodarone was similar to that seen with rate control drugs.
- Flecainide was highly effective in restoring sinus rhythm in this study.

International Journal of Cardiology 172; 2014:588–594
To investigate the clinical effectiveness and cost-effectiveness of

- pill-in-the-pocket (PiP) approach;
- in-hospital treatment (IHT);
- continuous antiarrhythmic drugs (AADs) for the treatment of patients with PAF.
The model results indicate that the PiP strategy is slightly less effective (in terms of QALY) than the other two strategies, but also less costly.

A PiP strategy seems to be more efficacious and cost-effective than an AAD strategy in men over 65 years and women over 70 years, but this is principally due to a very slight difference in QALY gained by the PiP strategy.

The AAD strategy, despite its low recurrence rate compared to PiP and IHT, shows the highest number of adverse events.

The AAD strategy has a very poor probability of being cost-effective under any threshold.
Because termination of AF may be associated with bradycardia due to sinus node or AV node dysfunction or a proarrhythmic response, **an initial conversion trial in a monitored setting is recommended** before this approach is used in the unmonitored outpatient setting.

- A beta blocker or non-dihydropyridine calcium channel antagonist should be administered >30 minutes before administering the **Vaughan Williams class IC agent** to prevent a rapid ventricular response due to 1:1 AV conduction during atrial flutter.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Oral</td>
<td>200–300 mg × 1†</td>
<td>Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Oral</td>
<td>450–600 mg × 1†</td>
<td>Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2014;64:e1-76.
In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide (200–300 mg) or propafenone (450 – 600 mg) can be self-administered by the patient at home (‘pill in the pocket’ therapy) to restore sinus rhythm, after safety has been established in the hospital setting.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>1st dose</th>
<th>Follow-up dose</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Oral</td>
<td>200–300 mg</td>
<td>N/A</td>
<td>Hypotension, atrial flutter with 1:1 conduction, QT prolongation. Avoid in patients with IHD and/or significant structural heart disease.</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>1.5–2 mg/kg over 10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>IV</td>
<td>1.5–2 mg/kg over 10 min</td>
<td></td>
<td>Hypotension, atrial flutter with 1:1 conduction, QRS prolongation (mild). Avoid in patients with IHD and/or significant structural heart disease.</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>450–600 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Europace. 2016;18:1609-1678
‘Pill in the pocket’ cardioversion in ‘low burden’ AF patients
The ‘pill-in-the-pocket’ approach. How to start with Class IC drugs?

Prior to initiating Class IC AADs, patients should be checked for contraindications including:

- structural heart disease;
- second- or third-degree AV block;
- left bundle branch block;
- right bundle branch block (when associated with left hemiblock);
- Brugada pattern;
- asymptomatic non-sustained ventricular tachycardia;
- cardiogenic shock;
- reduced LVEF <35%;
- post-MI; and
- significant renal or hepatic impairment.
The ‘pill-in-the-pocket’ approach. How to start with Class IC drugs?

- Oral flecainide and propafenone should be initially administered in a hospital setting with rhythm monitoring.
- Electrocardiogram parameters determined should include PR, QT, and QRS interval prolongation (≤120 ms).
- In addition, the presence of ischemia and tolerance to exercise should be determined.
- After initiation of Class IC AADs, use-dependent QRS widening may be assessed during a formal exercise test.
- During treatment, the QRS interval should be regularly monitored.
- If QRS widening occurs by more than 25% compared to baseline, the dosage should be reduced or the drug should be discontinued until the ECG reverts to normal.
Intravenous administration of flecainide or propafenone in patients with recent-onset AF does not predict adverse effects during ‘pill-in-the-pocket’ treatment

- This study aimed to investigate whether tolerance to intravenous administration of flecainide or propafenone could predict the safety of the pill-in-the-pocket approach.

- Patients were discharged on pill-in-the-pocket treatment: 23 were given flecainide (16: 300 mg; 7: 200 mg) and 99 propafenone (76: 600 mg; 23: 450 mg).

- The mean follow-up period was 11 months. Of the 122 patients, 36 (30%) did not have any arrhythmic recurrences during the follow-up period, while 86 (70%) reported a total of 262 episodes of palpitations with abrupt onset, 213 of which (81%) were treated by 79 patients with either flecainide (in 20 patients) or propafenone (in 59 patients).

- **Flecainide was effective in 47 out of 49 episodes (96%) and propafenone in 154 out of 164 (94%).**

Heart 2010;96:546-549.
Major adverse effects after self-administration of Class 1C AADs

- In four (5%) of these patients, the adverse effects occurred during the first out-of-hospital self-administration of propafenone (one syncope, two presyncope, one sinus arrest).

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Mild heart disease</th>
<th>Drug</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Female</td>
<td>70</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Syncope due to A-V block</td>
</tr>
<tr>
<td>2.</td>
<td>Male</td>
<td>80</td>
<td>No</td>
<td>Propafenone 600 mg</td>
<td>Presyncope due to hypotension</td>
</tr>
<tr>
<td>3.</td>
<td>Male</td>
<td>75</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Presyncope</td>
</tr>
<tr>
<td>4.</td>
<td>Female</td>
<td>78</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Sinus arrest</td>
</tr>
</tbody>
</table>

Heart 2010;96:546-549.
Class IC AADs and proarrhythmia
potential for proarrhythmic effects of class 1C AADs

- Class 1C AADs may cause supraventricular proarrhythmia during AF through a regulatory effect on atrial fibrillatory activity, leading to slow atrial flutter typically at a rate of 200 bpm (1C flutter).

- Atrial fibrillation conversion to flutter is considered proarrhythmia.

- **Class 1C AADs does not slow AV conduction** and, as a result, a 1:1 ratio of AV conduction to high ventricular rate may occur. Atrioventricular nodal blocking drugs should be used to prevent 1:1 conduction and patients should be instructed to halt exercise when AF recurs.

- **Class 1C ventricular proarrhythmia manifests as monomorphic or as polymorphic ventricular tachycardia or fibrillation.**
The CAST trial

- Post-MI patients.
- CAST results have associated flecainide with increased mortality due to a greater incidence of ventricular fibrillation in this population (the so-called proarrhythmic effect).
- As a result, flecainide is not recommended for use in patients with CAD and/or depressed ventricular function.
- Which factors are involved in late, out-of-hospital proarrhythmia or sudden death during IC drug therapy is not clear.
- Several factors were implicated in CAST:
  - late development of ischemia;
  - congestive heart failure; and
  - accumulation of the drug to toxic levels.

The CAST trial

The CASH trial

- Small randomized trial of survivors of cardiac arrest: 59 pts in ICD arm vs. 59 pts in propafenone arm.
- 80 % CAD patients (mean LVEF 42%).

Am J Cardiol 1993;7:109-II3
Ventricular proarrhythmic risk factors related to Class 1C AADs

- Structural heart disease (CAD);
- Low LVEF (CHF);
- Wide QRS (>120 ms or >150% from baseline);
- Brugada ECG sign;
- Severe renal or hepatic failure
- High rate (use-dependent effect);
- High dose;
- Hypokalaemia.
In a substudy of AFFIRM trial, a left ventricular ejection fraction of less than 40% was associated with proarrhythmic events.
Data about safety and effectiveness of single-dose flecainide for cardioversion in patients at elevated cardiovascular risk are lacking

- 106 patients with recent onset AF and known structural heart disease (35.6% with CAD, 25% with MI and 17.0% with DCM) and/or elevated PROCAM-score received oral flecainide 300 mg for cardioversion.

- Patients with myocardial infarction in the past 6 months were excluded.

<table>
<thead>
<tr>
<th></th>
<th>Al 1 (n = 106)</th>
<th>Converted (n = 43; 40.6%)</th>
<th>Not-converted (n = 63; 59.4%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/men (%)</td>
<td>29/76 (27/73)</td>
<td>10/33 (34/43)</td>
<td>19/44 (66/57)</td>
<td>0.44</td>
</tr>
<tr>
<td>Age</td>
<td>66.14 ± 1.12</td>
<td>64.30 ± 1.68</td>
<td>67.40 ± 1.49</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI</td>
<td>26.63 ± 0.34</td>
<td>26.70 ± 0.51</td>
<td>26.58 ± 0.46</td>
<td>0.86</td>
</tr>
<tr>
<td>Heart rate per minute</td>
<td>102.79 ± 2.51</td>
<td>107.63 ± 4.15</td>
<td>99.49 ± 3.09</td>
<td>0.11</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>5.95 ± 0.42</td>
<td>6.23 ± 0.64</td>
<td>5.76 ± 0.57</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>58 (55.2)</td>
<td>21 (36.2)</td>
<td>37 (63.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>36 (35.6)</td>
<td>13 (36.1)</td>
<td>23 (63.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>27 (25.5)</td>
<td>12 (44.4)</td>
<td>15 (55.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>7 (6.6)</td>
<td>3 (42)</td>
<td>4 (58)</td>
<td>0.90</td>
</tr>
<tr>
<td>DCM (%)</td>
<td>19 (17.9)</td>
<td>6 (31.6)</td>
<td>13 (68.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>LVEF &lt; 35%</td>
<td>23 (21.7)</td>
<td>8 (34.8)</td>
<td>15 (65.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.13 ± 0.04</td>
<td>4.05 ± 0.07</td>
<td>4.19 ± 0.05</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Data about safety and effectiveness of single-dose flecainide for cardioversion in patients at elevated cardiovascular risk are lacking.

- In 43 of 106 patients (40.6%), sinus rhythm could be restored within 192.4 ± 10.7 min by flecainide.
- Life-threatening arrhythmias did not occur in any patient.
- When monitored properly (in-hospital), flecainide is safe and useful for cardioversion in patients at elevated cardiovascular risk.
Mortality and Class IC AADs. The Cochrane database.

- Very little data on mortality exist for class IC drugs.
- Data on three small randomized trials (146 patients in total) on flecainide that fulfilled the inclusion criteria demonstrated no deaths related to the drug.
- In one recent randomized trial (Flec-SL 2012) including more patients (362 patients followed at 6 months), no deaths were reported in any treatment group.
- In five trials (998 patients), no deaths in patients taking propafenone were reported.

Meta-analysis of flecainide safety in patients with supraventricular arrhythmias; University of York, NHS

- 122 studies
  - 26 double-blind randomized controlled trials (RCTs; 15 were placebo-controlled),
  - 25 RCTs without blinding, and
  - 71 uncontrolled studies.
- Total mortality in the flecainide group was 0.166% and the mortality rate per 100 patients years was 0.397 (95% CI: 0.172, 0.781).
- In relation to exposure time, the difference in deaths between the two groups was not statistically significant (P=0.46).
- Proarrhythmic episodes were significantly rarer in the flecainide group (2.7%) than in the controls (4.8%), (P=0.001).

Arzneimittel-Forschung 2002; 52: 507-514
All patients admitted with AF in Denmark from 1995 to 2004 and their subsequent use of AADs were identified by individual-level linkage of nationwide registries. Multivariable Cox proportional-hazard models with time-dependent covariates were used to analyse the risk of death associated with AAD therapy. A total of 141 500 patients were included in the study; of these 3356 (2.4%) patients received treatment with flecainide, 3745 (2.6%) propafenone, 23 346 (16.5%) sotalol, and 10 376 (7.3%) amiodarone. **Annualized mortality rates were 2.54, 4.25, 5.29, and 7.42 per year per 100 person years for flecainide, propafenone, sotalol, and amiodarone, respectively.** Multivariable Cox proportional-hazard models did not show increased risk of death associated with any of the AADs. Hazard ratio (95% confidence interval) for flecainide 0.38 (0.32–0.44), propafenone 0.65 (0.58–0.71), sotalol 0.65 (0.63–0.67), and amiodarone 0.94 (0.89–1.00).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean dosage (mg)</th>
<th>Average duration of follow-up (year)</th>
<th>Average duration of treatment (year)</th>
<th>All deaths during follow-up (%)</th>
<th>Deaths during treatment (%)</th>
<th>Deaths within 30 days of initiating treatment (%)</th>
<th>Annualized mortality rates (per year per 100 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>3356</td>
<td>205.6 ± 56.1</td>
<td>5.8</td>
<td>492 (14.7)</td>
<td>160 (4.8)</td>
<td>14 (0.4)</td>
<td>2.54</td>
</tr>
<tr>
<td>Propafenone</td>
<td>3745</td>
<td>411.4 ± 117.0</td>
<td>5.5</td>
<td>877 (23.4)</td>
<td>342 (9.1)</td>
<td>20 (0.5)</td>
<td>4.25</td>
</tr>
<tr>
<td>Sotalol</td>
<td>23 346</td>
<td>122.9 ± 49.7</td>
<td>5.2</td>
<td>6464 (27.7)</td>
<td>3145 (13.5)</td>
<td>192 (0.8)</td>
<td>5.29</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10 376</td>
<td>287.4 ± 87.9</td>
<td>4.2</td>
<td>3247 (31.3)</td>
<td>1779 (17.1)</td>
<td>212 (2.0)</td>
<td>7.42</td>
</tr>
<tr>
<td>Total cohort</td>
<td>141 500</td>
<td></td>
<td></td>
<td>62 173 (43.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AADs are safe in selected patients
What’s new in the Greek market?
RCTs that assessed efficacy of flecainide in cardioversion of recent-onset AF

Expert Opin Pharmacother. 2013;14:347-357
RCTs that assessed efficacy of flecainide in maintaining sinus rhythm in Patients with AF

Flecainide is highly effective in maintaining sinus rhythm in patients with paroxysmal AF

Expert Opin Pharmacother. 2013;14:347-357
Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL)

- After successful cardioversion, patients were randomly assigned in permuted blocks of six per centre to:
  - no antiarrhythmic drug treatment (control);
  - treatment with flecainide (200–300 mg per day) for 4 weeks (short-term treatment); or
  - treatment with flecainide for 6 months (long-term treatment).

Lancet 2012; 380: 238–46
Predictors of sinus rhythm after electrical cardioversion of atrial fibrillation: the Flec-SL trial data set

- Patients who were cardioverted back to sinus rhythm during oral pretreatment with flecainide for 48 h prior to scheduled electrical cardioversion were more than three times as likely to maintain sinus rhythm for 6 months after cardioversion.

- Pharmacological conversion of persistent AF with flecainide without the need for electrical cardioversion is a powerful and independent predictor of maintenance of sinus rhythm.
Predictors of sinus rhythm after electrical cardioversion of atrial fibrillation: the Flec-SL trial data set

Europace 2016
Comparison of the Safety and Efficacy of Flecainide vs. Propafenone

- 97 patients randomized to
  - Flecainide (max 300mg daily)
  - Propafenone (max 1200mg daily)

- In this study, **the probability for a patient to stay on flecainide after 1 year had a tendency to be higher than the probability to stay on propafenone.** This was related to the higher proportion of secondary effects leading to discontinuation of treatment in the propafenone group.

Am J Cardiol 1996; 77:66A-71 A
Long-term AADs therapy. Which is the best drug???

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean relapse rate (range)</th>
<th>Studies (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td>69% (44–85)</td>
<td>10</td>
</tr>
<tr>
<td>Quinidine</td>
<td>59% (46–89)</td>
<td>11</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>51% (46–56)</td>
<td>3</td>
</tr>
<tr>
<td>Propafenone</td>
<td>61% (54–70)</td>
<td>3</td>
</tr>
<tr>
<td>Flecainide</td>
<td>38% (19–51)</td>
<td>3</td>
</tr>
<tr>
<td>Sotalol</td>
<td>58% (51–63)</td>
<td>3</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>47% (17–64)</td>
<td>4</td>
</tr>
</tbody>
</table>
What about the SR flecainide?

- How to restore sinus rhythm in subjects taking flecainide SR?
Specific issues related to flecainide

Contraindications to flecainide?

- Prior to initiating Class IC AADs, patients should be checked for contraindications including:
  - structural heart disease;
  - second- or third-degree AV block;
  - left bundle branch block;
  - right bundle branch block (when associated with left hemiblock);
  - Brugada pattern;
  - asymptomatic non-sustained ventricular tachycardia;
  - cardiogenic shock;
  - reduced LVEF <35%;
  - post-MI; and
  - significant renal or hepatic impairment.

Renal or Hepatic Impairment

- Manifest hepatic functional impairment (liver failure) or renal impairment requires particular caution during treatment with flecainide.
- A lower starting dose at half the usual dosing recommendations, cautious increases of dosage and plasma level monitoring will often be necessary for patients with significant renal disease (creatinine clearance of <35 ml/min/1.73 m2). In patients with less severe renal disease the initial dosage may be as great as 100 mg every 12 hours.
- Since elimination of flecainide from plasma can be markedly slower in patients with significant hepatic impairment, treatment with flecainide should not be used in such patients unless the potential benefits clearly outweigh the risks.

Pharmacokinetics of flecainide

- Oral administration of flecainide results in extensive absorption (bioavailability: 90–95%).
- Flecainide does not appear to undergo significant hepatic first-pass metabolism; a 200–500mg daily dose produces plasma concentrations within the therapeutic range of 200 – 1000 mg/L (the maximum daily dose is 300 mg).
- The elimination half-life is 12 – 27 h.
- Flecainide undergoes extensive hepatic biotransformation via cytochrome P450 CYP2D6; inactive metabolites are excreted mostly (85%) in urine.
Take home messages

- The ‘pill-in-the-pocket’ strategy is effective in suitable patients with paroxysmal AF.
- The ‘pill-in-the-pocket’ strategy is less proarrhythmic and cost effective compared to continuous antiarrhythmic drugs (AADs) administration.
- Patients should meet pre-established criteria for safety reasons.
- Flecainide is effective and safe in paroxysmal AF patients.
- For the ‘pill in the pocket’ strategy, 200-300mg is the optimal dose of flecainide for sinus rhythm restoration in the setting of paroxysmal atrial fibrillation.
- For long-term protection, the recommended starting dose is 50 mg every 12 hours. The dose may be increased in increments of 50 mg b.d. at intervals of at least four days until efficacy is achieved. Most patients do not require more than 150 mg every 12 hours (300 mg/day) which is the maximum recommended daily dose.
Thank you very much for your attention

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Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/mL.