# Cardioversion of AF the pill-in-the-pocket

### J Mansourati Brest - France









### NO CONFLICT OF INTEREST TO DECLARE

arrhythmia is permitted to persist.<sup>--</sup> Electrical remodeling occurs rapidly and is characterized by shortened atrial refractoriness and loss of normal rate adaptation, which promotes AF occurrence. Contractile remodeling develops more insidiously and appears to arise from altered calcium transport and uptake and subsequent depression of the L-type calcium current.<sup>22</sup> Structural changes develop over a longer period of time and are characterized by diffuse scarring and chamber enlargement. Contractile and structural remodeling interferes with both atrial and ventricular function, and may be directly related to negative outcomes (e.g., thromboembolism, heart failure). Whereas electrical remodeling is typically reversible upon restoration of sinus rhythm, contractile and structural remodeling may persist. The longer the duration of AF, the

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#### Bunch J, Gersh BJ, JGIM 2010

### Mr V, 38 years



Restoring sinus rhythm in patients with atrial fibrillation

Three main objectives:

- 1) to find and treat a predisposing factor;
- 2) to prevent thromboembolic complications
- to cardiovert as soon as possible to avoid atrial remodeling and obtain SR more easily

### 1) Predisposing factors

- Chronic or acute alcohol intoxication (Holiday heart syndrome). 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 their 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.

### 2) Thromboembolic prevention

Risk factor	Score	
Congestive heart failure/LV dysfunction	1	
Hypertension	1	
Age ≥75	2	
Diabetes mellitus	<ul> <li>12</li> </ul>	
Stroka/TIA/thrombo-embolism	2	
Vascular disease*	1	
Age 65-74	1	
Sex category (i.e. female sex)	1	
Maximum score	9	

'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke,TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease <sup>a</sup>

### 3) Restoring SR

### Spontaneous conversion rates in placebo or rate-controlled studies of patients with recent-onset atrial fibrillation ≤7 days



Slavick, CJEM 2002

# **Paroxysmal AF** will convert earlier after initiation of the therapy than **persistent AF**.

#### Antiarrhythmic Drugs Vaughan-Williams Classification



#### FOR THE PILL-IN-THE-POCKET STRAT

Before any attempt to reduce AF, a predispos such as chronic or acute alcohol intoxication heart syndrome) should be assessed. In this car elimination will often lead to spontaneous re SR and no AAD will be needed if arrhythmia erated. Hyperthyroidism or hypokalaemia re

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#### Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Up to 7-d Duration

	Route of	Class of	Level of
Drug*	Administration	Recommendation	Evidence
Agents with proven efficacy	200.00	10	
Dofetilide	Oral	t	A
Flecainide	Oral or intravenous	1	A
Ibutilide	Intravenous	1	A
Propafenone	Oral or intravenous	1	A
Amiodarone	Oral or intravenous	lla	A
Less effective or incompletely studied agents			
Disopyramide	Intravenous	IIb	В
Procainamide	Intravenous	IIb	В
Quinidine	Oral	lib	В
Should not be administered			
Digoxin	Oral or intravenous	m	A
Sotalol	Oral or intravenous		A

ACC/AHA/ESC 2011 guidelines for the management of patients with atrial fibrillation.

### How to choose?

• AF duration

• Presence of structural heart disease

Pharmacological cardioversion with class I agents is possible within a time frame of **hours to a few days**, with decreasing efficacy after prolonged periods of AF



Gowda, Progress in Cardiovascular Diseases, 2005

**Class IC drugs** are more effective in converting shorter duration of AF.

If the arrhythmia episode <24 hours of duration, the conversion rate can be as high as 90% with intravenous administration of flecainide or propafenone. If AF is of longer duration, (days to weeks), the same drugs are less efficient (prolonged AF has remodeling as a prominent feature).

**Class III agents** are more efficient than class IC agents in cardioverting AF of longer duration

### Flecainide

- In most studies, flecainide has been administered as a short bolus infusion (10 min) at doses of 1 to 2 mg/kg
- Oral flecainide, 4mg/kg (maximum, 300 mg): cardioversion in 57-68% of the cases in 2-4 hours and 75-91% in 8 hours.
- Intravenous flecainide restored sinus rhythm more quickly than oral flecainide



HEART



Alp N J et al. Heart 2000;84:37-40

### Propafenone

- Efficacy of propafenone in converting recentonset AF to sinus rhythm within a few hours
- the expected conversion rate is between 41 and 91% after i.v. use (2 mg/kg over 10–20 min).
- The corresponding early conversion rates in placebo treated patients were 10–29%.
- Propafenone has only a limited efficacy for conversion of persistent AF and for atrial flutter



PARSIFAL Study Group, Am J Cardiol 1999

**propafenone** 600 mg with an additional dose of 300 mg after eight hours (43 pts)

1 mg digoxin IV followed by an oral loading of **quinidine** (400 mg followed by 200 mg every two hours) (38 pts)



DA Kosior, Cardiol J 2009

## Drugs and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phiebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecalnide	2 mg/kg i.v. over 10 min, or 200-300 mg p.o.	N/A	Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
lbutilide	1 mg Lx. over 10 min	I mg Lx over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450–600 mg p.o.		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg Lx. over 10 min after 15 min rest	So far only evaluated in clinical trials; recently approved. 48-304

### Indications for electrical and pharmacological cardioversion, and choice of AAD for pharmacological cardioversion in patients with recent-onset AF.

pharmacological and electrical cardioversion is shown in Figure 3.

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#### **Key Points**

- Vernakalant is effective in cardioversion of patients with AF  $\leq$ 7 days or AF  $\leq$ 3 days after cardiac surgery and provides a rapid antiarrhythmic effect with approximately 50% of patients converting within 90 minutes after the start of treatment and a median time to conversion of 8–14 minutes.
- Vernakalant is administered as a 10-minute infusion of 3 mg/kg and, if AF persists after 15 minutes, a second infusion of 2 mg/ kg can be given.
- Vernakalant has a satisfactory safety profile in patients with minimal-to-moderate heart disease, including ischaemic heart disease, but should be used with caution in haemodynamically stable patients with NYHA class I and II heart failure, because of increased risk of hypotension and non-sustained ventricular arrhythmias in these patients.
- Vernakalant is contraindicated in patients with hypotension <100 mmHg, recent (<30 days) acute coronary syndrome, NYHA class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (uncorrected QT >440 ms).

#### 7.1 Upstream therapy

In the last several years, a number of trials investi therapy for prevention of AF have been report the recent placebo-controlled, double-blind trials v receptor blockers (ARBs) and the majority of trials urated fatty acids failed to show convincing results. now very little reason to consider the use of such prevention of AF recurrence in patients with little c heart disease. It may still be justified to co-prescrit angiotensin-converting enzyme inhibitor with an drug to increase the likelihood of maintaining sin cardioversion.<sup>136</sup>

### 7.2 Principles of antiarrhythmic therapy

Oral antiarrhythmic drug therapy can be considered ment of recurrent (paroxysmal and persister meta-analyses and systematic reviews have confirn mic efficacy whilst raising signals of concern rela events and mortality.<sup>141–144</sup> For this reason, it is in phasise that antiarrhythmic drug therapy should or control resistant symptoms due to recurrent AF a Besides hypotension or bradycardia, amiodarone can cause QT prolongation and rarely torsades de pointes requiring ECG monitoring. According to the longer ed, after respecting contraindications, to ver ty during a hospitalization for a first attempt On the other hand, to avoid overuse of the

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For AF conversion, oral propatenone (single dose) was administered according to the weight of the patient: 600 mg if the patient weighed  $\geq$ 70 kg, or 450

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The efficacy of propafenone therapy was reproducible

Sinus rhythm was restored in 60 of 65 subjects (93%, p < 0.001)

The time interval between the onset of arrhythmia and the start of treatment was shorter during the second compared with the first AF episode (7.8 $\pm$ 3.2 vs 3.2 $\pm$  2.7 hours, respectively, p < 0.05).

**The mean conversion time was faster during the second (2.4±2.2 hours)** than during the first antiarrhythmic treatment (3.5±1.4 hours, p <0.05).

Asymptomatic pauses ≥ 2 seconds were observed at the time of sinus rhythm restoration in 7 patients (maximum 4.5 seconds); No ventricular proarrhythmic effects were observed. A Capucci, Am J Cardiol 2003 tion were associated with earlier sinus r ration. No sustained episodes ( $\geq 1 \text{ mini}$  flutter with atrioventricular conduction  $\leq$ tachycardia were detected. Asymptomatiseconds were observed at the time of s restoration in 7 patients (maximum 4.5 swas probably related to the presence of sinus node dysfunction. No ventricular pr effects were observed.

#### A single oral loading dose of propafe sidered first-line therapy for conversion onset AF. The success rate ranges from $\pm$

#### 1346 THE AMERICAN JOURNAL OF CARDIOL

A Capucci, Am J Cardiol 2003

### « Pill-in-the-Pocket » Approach

### Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach



#### Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach

Mean follow-up :15±5 months

Episodes of arrhythmia were treated 36±93 minutes after the onset of symptoms.

Treatment was successful in 534 episodes (94%);

The time to resolution of symptoms was 113±84 minutes.

Adverse effects by 12 patients (7%) : atrial flutter at a rapid ventricular rate in 1 patient noncardiac side effects in 11 patients.

The numbers of monthly visits to the ER and hospitalizations were significantly lower during FU than during the year before the target episode (P<0.001 for both comparisons).

### Pill-in-the-Pocket Approach

- For selected patients, self treatment strategy is feasible, safe, and reduces hospital admissions and emergency department visits
- Eligible patients should not have a history of left ventricular dysfunction and should not have valvular or ischaemic heart disease, and they should have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation

### Pill-in-the-Pocket Approach

 Patients should first be treated for symptoms at a specialist hospital unit (potential side effects), using oral flecainide or propafenone;

 if successful, the drug can be carried by the patient for self treatment when symptoms occur

### Pill-in-the-Pocket Approach

This strategy should be avoided in patients with:

- sinus or AV node dysfunction,
- bundle-branch block
- QT-interval prolongation,
- Brugada syndrome
- or structural heart disease

### **Concerns about anticoagulation**

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

### 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.