FIBRILLATION ATRIALE :
STRATEGIE ANTIARYTHMIQUE, CARDIOVERSION
(PHARMACOLOGIQUE ET ELECTRIQUE)

J.Y. LE HEUZEY

Hopital Georges Pompidou
Université René Descartes, Paris

DIU Rythmologie / Stimulation, 29 Janvier 2014
Projected number of adults with AF in the US over the period 1995-2050

N=756 patients with one ECG-AF episode or more at baseline
(PAF, n = 167; Chronic, n = 389; Recent Onset, n = 200)

THE COCAF STUDY
DISTRIBUTION OF COSTS

Total cost: 3209 € per year
FR = 2.5 Billion €
EU = 25 Billion €

Le Heuzey et al., Am. Heart J. 2004, 147: 121-6
Epidemiology of atrial fibrillation in France: Extrapolation of international epidemiological data to France and analysis of French hospitalization data

Épidémiologie de la fibrillation atriale en France : extrapolation à partir des données internationales et point sur les hospitalisations

Agnès Charlemagne a,*, Jacques Blacher b, Ariel Cohen c, Jean-Philippe Collet d, François Diévant e, Pascal de Groote f, Olivier Hanon g, Antoine Leenhardt h, Jean-François Pinel i, George Pisica-Donose j, Jean-Yves Le Heuzey k

Number of patients and hospitalizations (PMSI 2005-2008)

- Number of patients - principal
- Number of patients - associated
- Number of patients - Total
- Number of stays - principal
- Number of stays - associated
- Number of stays - Total

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients (+ 26% on 3 years)</th>
<th>Number of stays (+ 32% on 3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>100,000</td>
<td>150,000</td>
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<tr>
<td>2006</td>
<td>200,000</td>
<td>250,000</td>
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<td>2007</td>
<td>300,000</td>
<td>350,000</td>
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<td>2008</td>
<td>400,000</td>
<td>450,000</td>
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ATRIAL FIBRILLATION: WHICH TREATMENT?

I- PHARMACOLOGICAL THERAPY

- Antithrombo-embolic therapy:
  - vitamin K antagonists
  - antiplatelet drugs
  - heparin (s)
  - direct oral anticoagulants (antithrombin and antiXa)

- Antiarrhythmic therapy:
  - in cardioversion (pharmacological cardioversion or preparation to electrical cardioversion)
  - in maintenance of sinus rhythm
  - in rate control
ATRIAL FIBRILLATION: WHICH TREATMENT?
II- NON PHARMACOLOGICAL THERAPY

• Occluders
• Electrical cardioversion
• Ablation:
  • pulmonary vein isolation (+ atrial lines, defragmentation …)
  • A-V node (+ pacing)
• Pacing (bi-atrial, specific algorithms)
• Surgery (maze, thoracoscopy …)
CLASS I ANTI-ARRHYTHMIC DRUGS IN DEVELOPMENT (1984)

- Encainide
- Lorcanide
- Moricizine
- Pirmenol
- Penticainide
- Mesocainide
- Carocainide
- Tocainide
- Indocainide
- Recainam
- Diprafenone
- Nicainoprolol
Odds Ratio / Total mortality patients treated with quinidine / Control

RCT

- Boissel: 212
- Byrne-Quinn: 92
- Hartel: 175
- Hillestad: 100
- Lloyd: 53
- Sodermark: 176

All studies: N = 808

Coplen SE. Circulation. 1990; 82: 1106-1116.
Antiarrhythmic Agents Cardiac Mortality SPAF trial

- Stroke prevention in AF 1330 pts
- AAD (class I)
- RR of cardiac death in pts with CHF: 4.7 (p < 0.001, CI 1.9 -11.6)

Flaker et al JACC 1992; 20: 527
VAUGHAN – WILLIAMS CLASSIFICATION

- **Class I** : sodium inhibitors
  - Ia : Quinidine, Disopyramide
  - Ib : Lidocaïne, Mexiletine
  - Ic : Flecaïnide, Propafenone, Cibenzoline

- **Class II** : beta-blockers

- **Class III** : potassium blockers : Amiodarone, Sotalol

- **Class IV** : calcium inhibitors : Verapamil, Diltiazem
The Sicilian Gambit

A New Approach to the Classification of Antiarrhythmic Drugs Based on Their Actions on Arrhythmogenic Mechanisms

Task Force of the Working Group on Arrhythmias of the European Society of Cardiology

The Queen’s Gambit is an opening move in chess that provides a variety of aggressive options to the player electing it. This report represents a similar gambit (the Sicilian Gambit) on the part of a group of basic and clinical investigators who met in Taormina, Sicily to consider the classification of antiarrhythmic drugs. Paramount to their considerations were 1) dissatisfaction with the options offered by existing classification systems for inspiring and directing research, development, and therapy, 2) the disarray in the field of antiarrhythmic drug development and testing in this post–Cardiac Arrhythmia Suppression Trial (CAST) era, and 3) the desire to provide an operational framework for consideration of antiarrhythmic drugs that will both encourage advancement and have the plasticity to grow as a result of the advances that occur. The multifaceted approach suggested is, like the title of the article, a gambit. It is an opening rather than a compendium and is intended to challenge thought and investigation rather than to resolve issues. (Circulation 1991;84:1831–1851)
<table>
<thead>
<tr>
<th>DRUG</th>
<th>CHANNELS</th>
<th>RECEPTORS</th>
<th>PUMPS</th>
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<tr>
<td></td>
<td>Na</td>
<td>Ca</td>
<td>K</td>
</tr>
<tr>
<td>Lidocaine</td>
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<td></td>
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<tr>
<td>Mexiletine</td>
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<td>Tocainide</td>
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<td>Disopyramide</td>
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<td>Quinidine</td>
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<td>Propafenone</td>
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<td>Flecainide</td>
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<td>Bepridil</td>
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<td>Diltiazem</td>
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<td>Bretylium</td>
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<td>Sotalol</td>
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<td>Amiodarone</td>
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<td>Propranolol</td>
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<td>Atropine</td>
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<td></td>
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<tr>
<td>Adenosine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative blocking potency:
- ○: Low
- □: Moderate
- ●: High

Legend:
- ○: Agonist
- □: Agonist/Antag.
- A: Activated state blocker
- I: Inactivated state blocker
GAMBIT, n. Chess:

(it. Gambetto, trip)

a chess move early in the game in which the player sacrifices pieces in order to obtain an advantageous position
Primary end point: total mortality (all causes)

- **Rate**
- **Rhythm**

p = 0.078

**AFFIRM**
Atrial Fibrillation Follow-up Investigation of Rhythm Management
RACE study: composite end point

(cardiovascular mortality + thromboembolic complications + bleeding + implantation of a pacemaker + heart failure + severe adverse events of antiarrhythmic drugs)

Primary End Point: Cardiovascular Death

Logrank $p = 0.594$

Hazard ratio: $1.058$
(95% CI, 0.86 to 1.30)

- Rhythm control 182 (27%)
- Rate control 175 (25%)

Number at risk
- Rhythm control: 593, 514, 378, 228, 82
- Rate control: 604, 521, 381, 219, 69

RHYTHM OR RATE CONTROL?

- **Rhythm control better choice for**: younger patients, highly symptomatic patients or patients with few risk factors of relapse

- **Rate control better choice for**: older patients, asymptomatic patients or patients with few symptoms, patients with advanced underlying heart disease
### TABLE 3. Covariates Significantly Associated With Survival Results With Echocardiographic Data Excluded

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$P$</th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment*</td>
<td>&lt;0.0001</td>
<td>1.06</td>
<td>1.04</td>
<td>1.08</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>&lt;0.0001</td>
<td>1.65</td>
<td>1.31</td>
<td>2.07</td>
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<tr>
<td>Congestive heart failure</td>
<td>&lt;0.0001</td>
<td>1.83</td>
<td>1.45</td>
<td>2.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt;0.0001</td>
<td>1.56</td>
<td>1.22</td>
<td>2.00</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>&lt;0.0001</td>
<td>1.54</td>
<td>1.17</td>
<td>2.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>&lt;0.0001</td>
<td>1.75</td>
<td>1.29</td>
<td>2.39</td>
</tr>
<tr>
<td>First episode of atrial fibrillation</td>
<td>0.0067</td>
<td>1.27</td>
<td>1.01</td>
<td>1.58</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>&lt;0.0001</td>
<td>0.54</td>
<td>0.42</td>
<td>0.70</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>&lt;0.0001</td>
<td>0.47</td>
<td>0.36</td>
<td>0.61</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>&lt;0.0001</td>
<td>1.50</td>
<td>1.18</td>
<td>1.89</td>
</tr>
<tr>
<td>Rhythm-control drug use</td>
<td>0.0005</td>
<td>1.41</td>
<td>1.10</td>
<td>1.83</td>
</tr>
</tbody>
</table>

*Per year of age.
We included physically active patients, rather than sedentary patients, in our trial, because we chose to assess rate control by means of exercise testing in the strict-control group. Thus, we expected a higher incidence of heart failure in the lenient-control group and in 18 of the 195 patients (9.3%) required hospitalization for heart failure. This figure was lower in the strict-control group (6.3%).

The cumulative incidence of the primary outcome at 3 years was 14.9% in the strict-control group, as compared with 12.9% of patients in the lenient-control group (P = 0.02 for noninferiority). In the lenient-control group, as compared with 14.9% of patients in the strict-control group, the target rate was virtually always exceeded. Approximately half the deaths in our study were related to heart failure. Third, the rate of adverse effects of drugs, other than syncope, and pacemaker implantation was similar across heart-rate categories at the end of the dose-adjustment phase (Table B in the Supplementary Appendix).

A major concern with rate control is the induction or worsening of underlying disease rather than to the heart rate itself. Although the prevalence of symptoms associated with exercise testing in the strict-control group. Thus, we expected a higher incidence of heart failure in the lenient-control group, and this occurred in 12.9% of patients in the lenient-control group and in 18 of the 195 patients (9.3%) required hospitalization for heart failure. This figure was lower in the strict-control group (6.3%).

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Choice of Strategy at Baseline by Cardiologists

- **Rate control strategy**: 45.1% (n=2528)
- **Rhythm control strategy**: 54.9% (n=3076)

Baseline Demographics and Comorbidities

n=5604

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate-control</th>
<th>Rhythm-control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity Caucasian</td>
<td>9%</td>
<td>9%</td>
<td>1.000</td>
</tr>
<tr>
<td>History of Myocardial Infarction</td>
<td>9%</td>
<td>9%</td>
<td>1.000</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>16%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History Diabetes</td>
<td>16%</td>
<td>16%</td>
<td>0.006</td>
</tr>
<tr>
<td>History Dyslipidemia</td>
<td>15%</td>
<td>16%</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>13%</td>
<td>10%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History Heart Failure</td>
<td>7%</td>
<td>13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF NYHA I + II</td>
<td>22%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History HTN</td>
<td>20%</td>
<td>24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History Stroke/TIA</td>
<td>7%</td>
<td>9%</td>
<td>0.006</td>
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<tr>
<td>History CAD</td>
<td>18%</td>
<td>20%</td>
<td>0.006</td>
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<tr>
<td>Fam. hist. Premature CV Disease</td>
<td>18%</td>
<td>20%</td>
<td>0.006</td>
</tr>
<tr>
<td>Lone AF</td>
<td>16%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p value compares the percentage of the condition between rhythm control vs. rate control

Clinical Presentation of AF at Baseline

- **Atrial fibrillation at inclusion**
  - Total: 57%
  - Rate-control: 81%
  - Rhythm-control: 39%

- **Sinus rhythm at inclusion**
  - Total: 43%
  - Rate-control: 63%
  - Rhythm-control: 20%

- **Symptomatic**
  - Total: 66%
  - Rate-control: 76%
  - Rhythm-control: 81%

- **Asymptomatic**
  - Total: 32%
  - Rate-control: 52%
  - Rhythm-control: 19%

- **AF persistent**
  - Total: 34%
  - Rate-control: 66%
  - Rhythm-control: 15%

- **AF paroxysmal**
  - Total: 52%
  - Rate-control: 68%
  - Rhythm-control: 32%

*p value <0.001 for all comparisons

Origin of atrial premature beats

Haissaguerre M et al.
Catheter Ablation for Atrial Fibrillation

Are Results Maintained at 5 Years of Follow-Up?

Rukshen Weerasooriya, BMEDSc(Hons), MBBS,*† Paul Khairy, MD, PhD,‡ Jean Litalien, MD,* Laurent Macle, MD,‡ Meleze Hocini, MD,* Frederic Sacher, MD,* Nicolas Lellouche, MD,* Sebastien Knecht, MD,* Matthew Wright, PhD, MD,* Isabelle Nault, MD,* Shinsuke Miyazaki, MD,* Christophe Scavee, MD,* Jacques Clementy, MD,* Michel Haissaguerre, MD,* Pierre Jais, MD*

*Bordeaux-Pessac, France; Crawley, Western Australia; and Montreal, Quebec, Canada

Figure 2 Single Procedure Success

Figure 3 Multiple Procedure Success
CABANA Pilot Study
Recurrence of Any AF, AFL, or AT

**HR 0.69 (0.37-1.32) P=0.264**

<table>
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<tr>
<th>Time (months)</th>
<th>Drug Rx</th>
<th>Ablation Rx</th>
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<tr>
<td>0</td>
<td>72%</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>(59)</td>
<td>(36)</td>
</tr>
<tr>
<td>6</td>
<td>(72)</td>
<td>(50)</td>
</tr>
<tr>
<td>9</td>
<td>(59)</td>
<td>(50)</td>
</tr>
<tr>
<td>12</td>
<td>(72)</td>
<td>(50)</td>
</tr>
</tbody>
</table>

Blanking period
... so what?

Number of patients: 600,000
Centers performing AF ablation: 20

Number of cardiologists: 5,000
Maximum number of patients / year: 15,600

2.6%!

*3 patients / day per center = 12h / day

Courtesy C. de Chillou
Dronedarone Significantly Decreased Risk of CV Hospitalisation or Death by 24%

Mean follow-up 21 ±5 months.

Patients at risk:

<table>
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<tr>
<th></th>
<th>Placebo</th>
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<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>30 months</th>
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<td>1625</td>
<td>1072</td>
<td>385</td>
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<td>1963</td>
<td>1776</td>
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</tbody>
</table>

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and/or aspirin and other antiplatelets therapy) and/or other cardiovascular agents such as ACEIs/ARBs and statins. Mean follow-up 21 ±5 months.


HR=0.76

24% reduction in relative risk

\( p < 0.001 \)
Primary Endpoint: More AF Events But Less Early Discontinuation With Dronedarone

Dronedarone
Amiodarone

<table>
<thead>
<tr>
<th>Number of patients with endpoint</th>
<th>Dronedarone (n=249)</th>
<th>Amiodarone (n=255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG documented AF endpoint</td>
<td>184 (73.9%)</td>
<td>141 (55.3%)</td>
</tr>
<tr>
<td>Documented AF after conversion</td>
<td>158 (63.5%)</td>
<td>107 (42.0%)</td>
</tr>
<tr>
<td>Unsuccessful electrical cardioversion</td>
<td>29 (11.6%)</td>
<td>16 (6.3%)</td>
</tr>
<tr>
<td>No spontaneous conversion and no electrical cardioversion on day 10 to day 28</td>
<td>38 (15.3%)</td>
<td>29 (11.4%)</td>
</tr>
<tr>
<td>Premature study drug discontinuation</td>
<td>26 (10.4%)</td>
<td>34 (13.3%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>1 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Intolerance</td>
<td>25 (10.0%)</td>
<td>34 (13.3%)</td>
</tr>
</tbody>
</table>

RRR (95%CI) = 1.589 (1.275;1.98)
p-value <0.001

Stroke, systemic embolism, myocardial infarction or cardiovascular death

<table>
<thead>
<tr>
<th>First Co-primary Outcome</th>
<th>Dronedarone</th>
<th>Placebo</th>
<th>Dronedarone vs placebo HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43 (2.7%)</td>
<td>19 (1.2%)</td>
<td>2.29 (1.34 – 3.94) p=0.002</td>
</tr>
</tbody>
</table>

Number at risk:

<table>
<thead>
<tr>
<th>Dronedarone</th>
<th>1619</th>
<th>1421</th>
<th>930</th>
<th>353</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1617</td>
<td>1445</td>
<td>908</td>
<td>377</td>
</tr>
</tbody>
</table>
AF may emerge along the CV continuum and is a contributing factor in many CV conditions

- Atherosclerosis and LVH
- Risk factors (diabetes, hypertension)
- Remodeling
- Ventricular dilation
- MI
- HF
- End-stage microvascular heart disease
- Death
- Atrial fibrillation

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)†

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

European Heart Journal

http://eurheartj.oxfordjournals.org/

Eur. Heart J. 2010; 31 : 2369 - 429
2012 Focused Update of the ESC Guidelines for the Management of Atrial Fibrillation

An update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation

Developed with the special contribution of the European Heart Rhythm Association

Authors/Task Force Members: A. John Camm (Chairperson) (UK)*, Dan Atar (Norway), Raffaele de Caterina (Italy), Gerhard Hindricks (Germany), Stephan H. Hohnloser (Germany), Paulus Kirchhof (Germany/UK), Gregory Y. H. Lip (UK), Irene Savelieva (UK)

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† Representing the European Association for Cardio-Thoracic Surgery (EACTS)

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Recommendations
Total = 210

Class of Recommendation
- Class I: 40%
- Class IIa: 35%
- Class IIb: 18%
- Class III: 7%

Level of Evidence
- LoE A: 51%
- LoE B: 33%
- LoE C: 16%
For patients in NYHA functional class III or IV, there is evidence from the ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse (ANDROMEDA) trial that these patients may derive harm from dronedarone therapy.

On the other hand, in patients with NYHA class I or II heart failure, or with HF-PEF, there is no clear scientific evidence for harmful effects of the drug. There was no clear signal from the subgroup analysis of PALLAS that the extent of heart failure (NYHA class) or degree of left ventricular systolic dysfunction (left ventricular ejection fraction) was relevant to any PALLAS endpoint, including heart failure hospitalizations or events. On the other hand, PALLAS recruited a high proportion of patients with a history of heart failure and various degrees of cardiac decompensation, except for NYHA class IV. Heart failure events in PALLAS were more common in patients with underlying coronary artery disease, but the statistical validity of this subgroup analysis is uncertain. Use of dronedarone as an antiarrhythmic agent in patients with recurrent AF and less severe heart failure (NYHA class I–II) is not appropriate unless there is no suitable alternative.

There was a signal in the PALLAS trial that dronedarone was associated with increased sudden mortality in patients on concomitant digoxin therapy; hence the combined use of these two drugs is discouraged. No proarrhythmia has been documented with the use of dronedarone in any trial and there are few or any reports of torsades de pointes or ventricular tachycardia in the post-approval adverse event reporting. Therefore, it seems unnecessary to remove this option for the treatment of hypertension with left ventricular hypertrophy, where the risk from antiarrhythmic drugs is thought to be related to torsades de pointes.

**Recommendations for oral antiarrhythmic agents**

| Class of recommendation | Level of evidence | Ref |
|-------------------------|----------------___|-----|
| Class **a** | **Level b** | **Ref C** |
| Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm. | I | 142, 144, 153 |
| Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g. those at risk for therapy-associated complications. | IIb | 145 |
| Dronedarone is not recommended in patients with permanent AF. | III | 5 |

**Figure 4** Choice of antiarrhythmic drug according to underlying pathology.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy, NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.
Amiodarone and the Risk of Cancer: A Nationwide Population-Based Study

Vincent Yi-Fong Su, MD; Yu-Wen Lin, BSc; Chia-Jen Liu, MD; Yu-Chin Lee, PhD; and Chia-Jen Liu, MD

BACKGROUND: In postmarketing surveillance, amiodarone was linked to malignant tumors, especially thyroid cancer, and skin cancer after amiodarone was marketed. To better understand the postulated cancer liabilities of amiodarone, the authors conducted a population-based cohort study. The study cohort included 6418 subjects, with a median follow-up of 2.57 years. A total of 280 patients developed cancer. The risk of cancer increased with the cumulative defined daily doses (cDDDs) of amiodarone. Multivariate analysis. The dose-effect was also confirmed with the multivariate analysis, and the difference between dose levels was not significant when different covariates representing age, sex, and comorbidities were adjusted. After adjustment for catastrophic illness is free from related medical costs, NHI is mandatory, and all Taiwanese residents can access health care. The results of the current study indicate that amiodarone may be associated with an increased risk of incident cancer, especially in males, with a dose-dependent effect. CONCLUSIONS: The results of the current study indicate that amiodarone may be associated with an increased risk of incident cancer, especially in males, with a dose-dependent effect. Cancer 2013;119:1699–705. © 2013 American Cancer Society.

KEYWORDS: amiodarone, cancer, malignancy, thyroid cancer, lung cancer.
The risk of antiarrhythmic drugs in atrial fibrillation: 20 years of controversies

Jean-Yves Le Heuzey*

Cardiologie A et Rythmologie, Hôpital Européen Georges Pompidou, Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, 20 Rue Leblanc, 75015 Paris, France

Received 8 June 2009; accepted after revision 9 June 2009

Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study

N=141500
DC shock delivered for first time in 1947 to treat a VF, routinely used to treat AF since 1967 (Lown)
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate DCC is recommended when a rapid ventricular rate does not respond promptly to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, angina, or heart failure.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Immediate DCC is recommended for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Elective DCC should be considered in order to initiate a long-term rhythm control management strategy for patients with AF.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success of DCC and prevent recurrent AF.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Repeated DCC may be considered in highly symptomatic patients refractory to other therapy.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Pre-treatment with β-blockers, diltiazem or verapamil may be considered for rate control, although the efficacy of these agents in enhancing success of DCC or preventing early recurrence of AF is uncertain.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>DCC is contraindicated in patients with digitalis toxicity.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
DCC: When?

1. **Recent-onset AF (<48 h)**
   - **Haemodynamic instability**
     - Yes: **Electrical cardioversion**
     - No: **Structural heart disease**
       - Yes: i.v. amiodarone
       - No: i.v. flecainide or i.v. propafenone i.v. ibutilide
AF for cardioversion

AF onset <48 h

Yes

AF for cardioversion

Heparin

Cardioversion

SR

No long-term OAC

AF

Risk factors

Consider if long-term OAC indicated

No

Long-term OAC indicated

No

Risk factors

Yes

Yes

3 weeks therapeutic OAC

TOE strategy

Heparin

No LAA thrombus

LAA thrombus

Opt for rate control if LAA thrombus still present

Therapeutic OAC for 3 weeks

Conventional OAC or TOE

*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present.

1 Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus.
Anesthetist assessment before cardioversion

- Digoxin, K+, INR, … before cardioversion
- Fasting and steady state, perfused, reanimation room
- Short duration anesthesia (Propofol, 1cc/10Kg)
- Adhesive + gelled electrodes +++
- Rhythm, arterial pressure, O² saturation, permanent monitoring, up to 3 h after the shock

Adapted from S. Boveda
- Electrodes diameter (inverse relationship between surface and impedance/current density): **8 to 12 cm**

- Electrode / skin interface: **gelled electrodes**

- Anteroposterior positioning: 2nd et 3rd right intercostal spaces / left scapula angulus: 50% less energy (Lown, 1964)

- Avoid sternum and vertebrae (high impedance): 96% of energy delivered away from the heart

- **3 biphasic shocks** (if necessary) for every session

- First shock delivered at 100 J if normal weighted patient and AF < 1 year, then increase energy until 200 J

Adapted from S. Boveda
Cardioversion in patients with pacemakers and ICDs

- The electrode paddle should be at least 8 cm from the battery, and the anteroposterior positioning is recommended.

- Biphasic shocks are preferred because they require less energy for AF termination.

- In pacemaker-dependent patients, an increase in pacing threshold should be anticipated.

- After cardioversion, the device should be interrogated and evaluated to ensure normal function.

Adapted from S. Boveda
« biphasic shock has greater efficacy, requires fewer shocks and lower delivered energy, than a monophasic shock » R. Page, JACC 2002
“The anteroposterior (right anterior, left posterior) defibrillator paddle position is superior to the anterolateral location.”

GL Botto, Heart 1999
## DCC / Primary Success Rate Factors

<table>
<thead>
<tr>
<th></th>
<th>Unsuccessful cardioversion (n = 20)</th>
<th>Successful cardioversion (n = 281)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (70%)</td>
<td>169 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (10)</td>
<td>62 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75 (14)</td>
<td>76 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heart disease</td>
<td>4 (20%)</td>
<td>67 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>6 (30%)</td>
<td>75 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>10 (50%)</td>
<td>139 (49%)</td>
<td>NS</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>193 (229)</td>
<td>80 (109)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous AF episodes</td>
<td>13 (65%)</td>
<td>137 (49%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial diameter (mm)</td>
<td>43 (7)</td>
<td>45 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50 (13)</td>
<td>52 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiarrhythmic drug treatment</td>
<td>13 (65%)</td>
<td>183 (65%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

GL Botto, Heart 1999
DCC : COMPLICATIONS

- **Stroke risk** if poor anticoagulation (1 to 7%)
- **VF** if wrong R wave synchrononization, hypoK+, digitalic overload, or myocardial ischaemia...
- Beware of **refractory VF** if digitalic overload+++ 
- **Bradycardia** if SSS or AV block (be careful if slow AF or AAD associations...)
- **Myocardial injury**: high energy iterative shocks (>400 Joules) and small diameter electrodes (Warnes, 1975)
- **Pacemaker or ICD** dysfunction

Adapted from S. Boveda
DCC : effective, safe and easy-to-do AF treatment

Very low risk of complications if guidelines are respected

Ambulatory feasibility

3 hours post cardioversion monitoring

Higher success rate when cardioversion is done early

AAD in order to enhance DCC and prevent recurrences...

OAC at least 3 weeks after cardioversion, depending on CHA₂DS²-VASc score...

AF recurrence risk : remains 50% at 1 year...

Courtesy S. Boveda
## RECOMMENDATIONS FOR PHARMACOLOGICAL CARDIOVERSION

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the ‘pill-in-the-pocket’ approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure, ibutilide may be considered. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during and for 4 h after the infusion because of risk of proarrhythmia.</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), other β-blocking agents and ajmaline (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
CONCLUSIONS

In a selected, risk-stratified population of patients with recurrent atrial fibrillation, pill-in-the-pocket treatment is feasible and safe, with a high rate of compliance by patients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions.

Flecainide or Propafenone « pill in the pocket »

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>59±11</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>122 (58)</td>
</tr>
<tr>
<td>Mild heart disease — no. (%)</td>
<td>92 (44)</td>
</tr>
<tr>
<td>History of atrial fibrillation — yr</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4±5</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Symptomatic episodes of atrial fibrillation in previous year</td>
<td>3.3±2.6</td>
</tr>
<tr>
<td>— no./patient†</td>
<td></td>
</tr>
<tr>
<td>Emergency room contacts in previous year — no./patient†</td>
<td>2.7±2.3</td>
</tr>
<tr>
<td>Hospitalizations in previous year — no./patient†</td>
<td>0.9±1.1</td>
</tr>
<tr>
<td>Duration of target episode before in-hospital treatment — min</td>
<td>280±368</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>120</td>
</tr>
<tr>
<td>Previous prophylactic treatment — no. of patients (%)</td>
<td>72 (34)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td>59±5</td>
</tr>
<tr>
<td>Left atrial diameter — mm</td>
<td>39±5</td>
</tr>
</tbody>
</table>
Vernakalant (RSD 1235):

- Class III antiarrhythmic drug mainly acting on Ikur (preferential effect on atrium), but owning also Na blocking effect

- Other drugs: AVE0118, S9947/S20951, NP142, Xen-D0101/2
In those patients who converted to sinus rhythm:

- Conversion was successful with the first dose in ~75%
- 97.2% of patients remained in sinus rhythm at 24 hours (pooled analysis of ACT I and ACT III studies)

The median time to conversion to sinus rhythm with vernakalant was 11 minutes (pooled analysis of ACT I and ACT III studies)

Vernakalant was not successful in terminating primary atrial flutter
## Drugs and doses for pharmacological conversion of (recent-onset) AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Follow-up dose</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>5 mg/kg i.v. over 1 h</td>
<td>50 mg/h</td>
<td>Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg/kg i.v. over 10 min, or 200-300 mg p.o.</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg i.v. over 10 min</td>
<td>1 mg i.v. over 10 min after waiting for 10 min</td>
<td>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.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>2 mg/kg i.v. over 10 min, or 450-600 mg p.o.</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>3 mg/kg i.v. over 10 min</td>
<td>Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest</td>
<td>So far only evaluated in clinical trials; recently approved*.</td>
</tr>
</tbody>
</table>

*ESC GUIDELINES 2010*
Recommendations for pharmacological cardioversion of recent-onset AF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When pharmacological cardioversion is preferred and there is no or minimal</td>
<td>I</td>
<td>A</td>
<td>120, 121,</td>
</tr>
<tr>
<td>structural heart disease, intravenous flecainide, propafenone, ibutilide, or</td>
<td></td>
<td></td>
<td>123, 124,</td>
</tr>
<tr>
<td>vernakalant are recommended.</td>
<td></td>
<td></td>
<td>126, 127,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>131–134</td>
</tr>
<tr>
<td>In patients with AF ≤7 days and moderate structural heart disease [but without</td>
<td>IIb</td>
<td>B</td>
<td>120, 121,</td>
</tr>
<tr>
<td>hypotension &lt;100 mm Hg, NYHA class III or IV heart failure, recent (&lt;30 days)</td>
<td></td>
<td></td>
<td>124, 128</td>
</tr>
<tr>
<td>ACS, or severe aortic stenosis], intravenous vernakalant may be considered.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vernakalant should be used with caution in patients with NYHA class I–II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart failure.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous vernakalant may be considered for cardioversion of postoperative</td>
<td>IIb</td>
<td>B</td>
<td>122</td>
</tr>
<tr>
<td>AF ≤3 days in patients after cardiac surgery.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; AF = atrial fibrillation; LoE = level of evidence;
NYHA = New York Heart Association.

\(^a\)Class of recommendation.

\(^b\)Level of evidence.

\(^c\)References.
patients with NYHA I or II heart failure because of increased risk of hypotension. At present, vernakalant should be avoided in patients with reduced LVEF (≤ 35%) because of limited experience.

The integration of vernakalant into the general schema for pharmacological and electrical cardioversion is shown in Figure 3.

**Key Points**

† Vernakalant is effective in cardioversion of patients with AF ≤ 7 days or AF ≤ 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. Oral antiarrhythmic drug therapy

7.1 Upstream therapy

In the last several years, a number of trials investigating upstream therapy for prevention of AF have been reported.

All of the recent placebo-controlled, double-blind trials with angiotensin-receptor blockers (ARBs) and the majority of trials with polyunsaturated fatty acids failed to show convincing results.

There is now very little reason to consider the use of such therapy for the prevention of AF recurrence in patients with little or no underlying heart disease. It may still be justified to co-prescribe an ARB or an angiotensin-converting enzyme inhibitor with an antiarrhythmic drug to increase the likelihood of maintaining sinus rhythm after cardioversion.

7.2 Principles of antiarrhythmic drug therapy

Oral antiarrhythmic drug therapy can be considered for the treatment of recurrent (paroxysmal and persistent) AF. Several meta-analyses and systematic reviews have confirmed antiarrhythmic efficacy whilst raising signals of concern related to adverse events and mortality.

For this reason, it is important to emphasise that antiarrhythmic drug therapy should only be offered to control resistant symptoms due to recurrent AF and that a safety

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*Figure 3* Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF.
Type of Cardioversion

By country

[Bar chart showing the percentage of pharmacological vs. electrical cardioversion for different countries.]

- Total: 34% Pharmacological, 66% Electrical
- Australia: 35% Pharmacological, 65% Electrical
- Brazil: 44% Pharmacological, 56% Electrical
- France: 16% Pharmacological, 84% Electrical
- Germany: 10% Pharmacological, 91% Electrical
- Italy: 41% Pharmacological, 59% Electrical
- Netherlands: 23% Pharmacological, 77% Electrical
- Poland: 50% Pharmacological, 50% Electrical
- Spain: 94% Pharmacological, 6% Electrical
- Sweden: 96% Pharmacological, 4% Electrical
- UK: 15% Pharmacological, 85% Electrical
Drugs administered for Pharmacological Cardioversion
By country

<table>
<thead>
<tr>
<th>Country</th>
<th>Amiodarone</th>
<th>Flecaïnide</th>
<th>Propafenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>54%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Australia</td>
<td>53%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Brazil</td>
<td>88%</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>France</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Germany</td>
<td>48%</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Italy</td>
<td>41%</td>
<td>39%</td>
<td>27%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>32%</td>
<td>77%</td>
<td>19%</td>
</tr>
<tr>
<td>Poland</td>
<td>53%</td>
<td>55%</td>
<td>5%</td>
</tr>
<tr>
<td>Spain</td>
<td>55%</td>
<td>41%</td>
<td>9%</td>
</tr>
<tr>
<td>Sweden</td>
<td>36%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>UK</td>
<td>70%</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

International Registry on Cardioversion for Atrial Fibrillation
CONCLUSIONS

1- The choice of rhythm or rate control strategy is, in most of the cases, an individual decision.

2- Sinus rhythm remains linked to a better prognosis, but its maintenance must be obtained by drugs without severe adverse effects or procedures without major complications.

3- Cardioversion keeps a major place in atrial fibrillation management but there are important discrepancies in the practices between countries.

5- Electrical is safer than pharmacological cardioversion but Vernakalant seems to be a promising alternative in recent atrial fibrillations.