

# La place du Dabigatran

## Données de la littérature

### Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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N Engl J Med 2009;361:1139-51.

*Les AVK diminuent efficacement (64 %) le risque thromboembolique en cas de FA mais sont complexes d'utilisation et exposent à un sur-risque hémorragique*

*Les AVK sont sous-utilisés: 50 % des patients non traités*

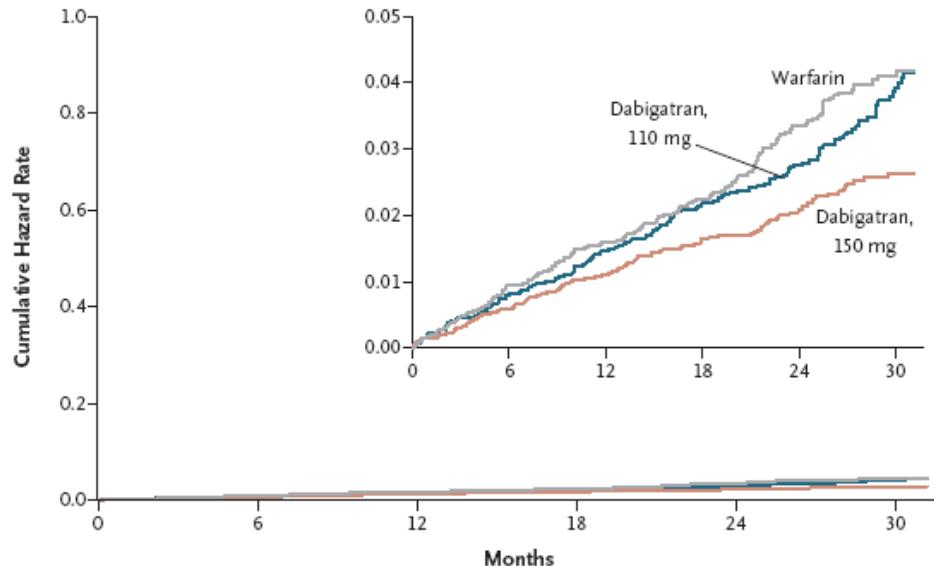
*>>> Nécessité d'un nouvel agent antithrombotique efficace, facile à prescrire et suivre et sûr.*

1

Le dabigatran = inhibiteur direct de la thrombine

18,113 patients who had AF and a risk of stroke randomly assigned to fixed doses of dabigatran 110 mg or 150 mg twice daily or, adjusted-dose warfarin

Mean Follow-up 20 mo



| No. at Risk        | Warfarin | 5862 | 5718 | 4593 | 2890 | 1322 |
|--------------------|----------|------|------|------|------|------|
| Dabigatran, 110 mg | 6015     | 5862 | 5710 | 4593 | 2945 | 1385 |
| Dabigatran, 150 mg | 6076     | 5939 | 5779 | 4682 | 3044 | 1429 |

**Figure 1.** Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.

Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

**Table 2.** Efficacy Outcomes, According to Treatment Group.

| Event                        | Dabigatran, 110 mg<br>(N = 6015) |      | Dabigatran, 150 mg<br>(N = 6076) |      | Warfarin<br>(N = 6022) |      | Dabigatran, 110 mg,<br>vs. warfarin |                                 | Dabigatran, 150 mg,<br>vs. Warfarin |                                   | Dabigatran,<br>150 mg vs. 110 mg |         |
|------------------------------|----------------------------------|------|----------------------------------|------|------------------------|------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|----------------------------------|---------|
|                              | no. of patients                  | %/yr | no. of patients                  | %/yr | no. of patients        | %/yr | Relative Risk<br>(95% CI)           | P Value                         | Relative Risk<br>(95% CI)           | P Value                           | Relative Risk<br>(95% CI)        | P Value |
| Stroke or systemic embolism* | 182                              | 1.53 | 134                              | 1.11 | 199                    | 1.69 | 0.91 (0.74–1.11)                    | <0.001 for noninferiority, 0.34 | 0.66 (0.53–0.82)                    | <0.001 for noninferiority, <0.001 | 0.73 (0.58–0.91)                 | 0.005   |
| Stroke                       | 171                              | 1.44 | 122                              | 1.01 | 185                    | 1.57 | 0.92 (0.74–1.13)                    | 0.41                            | 0.64 (0.51–0.81)                    | <0.001                            | 0.70 (0.56–0.89)                 | 0.003   |
| Hemorrhagic                  | 14                               | 0.12 | 12                               | 0.10 | 45                     | 0.38 | 0.31 (0.17–0.56)                    | <0.001                          | 0.26 (0.14–0.49)                    | <0.001                            | 0.85 (0.39–1.83)                 | 0.67    |
| Ischemic or unspecified      | 159                              | 1.34 | 111                              | 0.92 | 142                    | 1.20 | 1.11 (0.89–1.40)                    | 0.35                            | 0.76 (0.60–0.98)                    | 0.03                              | 0.69 (0.54–0.88)                 | 0.002   |
| Nondisabling stroke          | 60                               | 0.50 | 44                               | 0.37 | 69                     | 0.58 | 0.86 (0.61–1.22)                    | 0.40                            | 0.62 (0.43–0.91)                    | 0.01                              | 0.72 (0.49–1.07)                 | 0.10    |
| Disabling or fatal stroke    | 112                              | 0.94 | 80                               | 0.66 | 118                    | 1.00 | 0.94 (0.73–1.22)                    | 0.65                            | 0.66 (0.50–0.88)                    | 0.005                             | 0.70 (0.53–0.94)                 | 0.02    |
| Myocardial infarction        | 86                               | 0.72 | 89                               | 0.74 | 63                     | 0.53 | 1.35 (0.98–1.87)                    | 0.07                            | 1.38 (1.00–1.91)                    | 0.048                             | 1.02 (0.76–1.38)                 | 0.88    |
| Pulmonary embolism           | 14                               | 0.12 | 18                               | 0.15 | 11                     | 0.09 | 1.26 (0.57–2.78)                    | 0.56                            | 1.61 (0.76–3.42)                    | 0.21                              | 1.27 (0.63–2.56)                 | 0.50    |
| Hospitalization              | 2311                             | 19.4 | 2430                             | 20.2 | 2458                   | 20.8 | 0.92 (0.87–0.97)                    | 0.003                           | 0.97 (0.92–1.03)                    | 0.34                              | 1.06 (1.00–1.12)                 | 0.04    |
| Death from vascular causes   | 289                              | 2.43 | 274                              | 2.28 | 317                    | 2.69 | 0.90 (0.77–1.06)                    | 0.21                            | 0.85 (0.72–0.99)                    | 0.04                              | 0.94 (0.79–1.11)                 | 0.44    |
| Death from any cause         | 446                              | 3.75 | 438                              | 3.64 | 487                    | 4.13 | 0.91 (0.80–1.03)                    | 0.13                            | 0.88 (0.77–1.00)                    | 0.051                             | 0.97 (0.85–1.11)                 | 0.66    |

« Stroke or systemic embolism occurred in 182 patients receiving 110 mg of dabigatran (1.53% per year), 134 patients receiving 150 mg of dabigatran (1.11% per year), and 199 patients receiving warfarin (1.69% per year) p<0.001 »

« The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). »

# La place du Dabigatran

## Recommandations 2010

### Accord FDA +++...

« Where oral anticoagulation is appropriate therapy, dabigatran may be considered, as an alternative to adjusted dose VKA therapy »

| Risk category  | CHA <sub>2</sub> DS <sub>2</sub> -VASc score | Recommended antithrombotic therapy   |
|--|--|--|
| One 'major' risk factor or $\geq 2$ 'clinically relevant non-major' risk factors | $\geq 2$                                     | OAC <sup>a</sup>   |
| One 'clinically relevant non-major' risk factor                                  | 1  | Either OAC <sup>a</sup> or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.                                |
| No risk factors  | 0  | Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin. |

*-If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0-2), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin)*

*-If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of  $\geq 3$ ), dabigatran etexilate 110 mg b.i.d. may be considered, in view of a similar efficacy in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and of major bleeding compared with VKA*

**Table 10** Clinical characteristics comprising the HAS-BLED bleeding risk score

| Letter | Clinical characteristic <sup>a</sup>             | Points awarded   |
|--------|--|------------------|
| H      | Hypertension                                     | 1                |
| A      | Abnormal renal and liver function (1 point each) | 1 or 2           |
| S      | Stroke   | 1                |
| B      | Bleeding   | 1                |
| L      | Labile INRs                                      | 1                |
| E      | Elderly (e.g. age >65 years)                     | 1                |
| D      | Drugs or alcohol (1 point each)                  | 1 or 2           |
|        |  | Maximum 9 points |

'Hypertension' is defined as systolic blood pressure >160 mmHg.

'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine  $\geq 200 \text{ mmol/L}$ .

'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement.

'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.

'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. < 60%).

'Drugs/alcohol use' refers to concomitant use of drugs, such as ASA, NSAID drugs, or alcohol abuse.

## Nouveau score de risque Hémorragique

Score HASBLED  $\geq 3$   
=  
Patients à haut risque  
Initiation du trt, suivi régulier

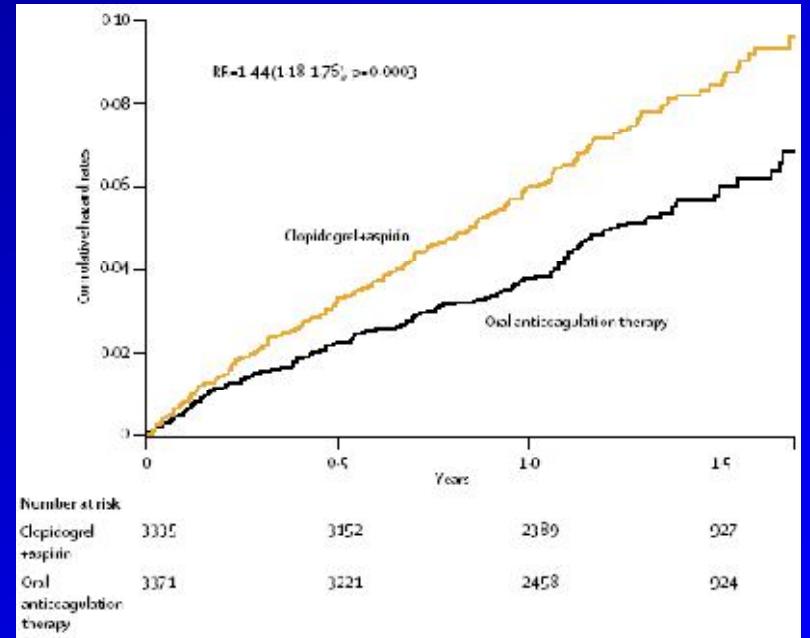
# La place de l'association Aspirine - Clopidogrel dans le traitement antithrombotique de la FA

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W):

Lancet 2006; 367: 1903-12

» AF + 1 or more risk factor for stroke, and were randomly allocated to receive OA (INR of 2·0-3·0; n=3371) or clopidogrel (75 mg per day) plus aspirin (75-100 mg per day recommended; n=3335).

» Primary outcome was 1st occurrence of stroke, non CNS systemic embolus, myocardial infarction, or vascular death.



« Combination therapy with aspirin 75-100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding. »

Classe IIa

6

Recommandations ESC 2010

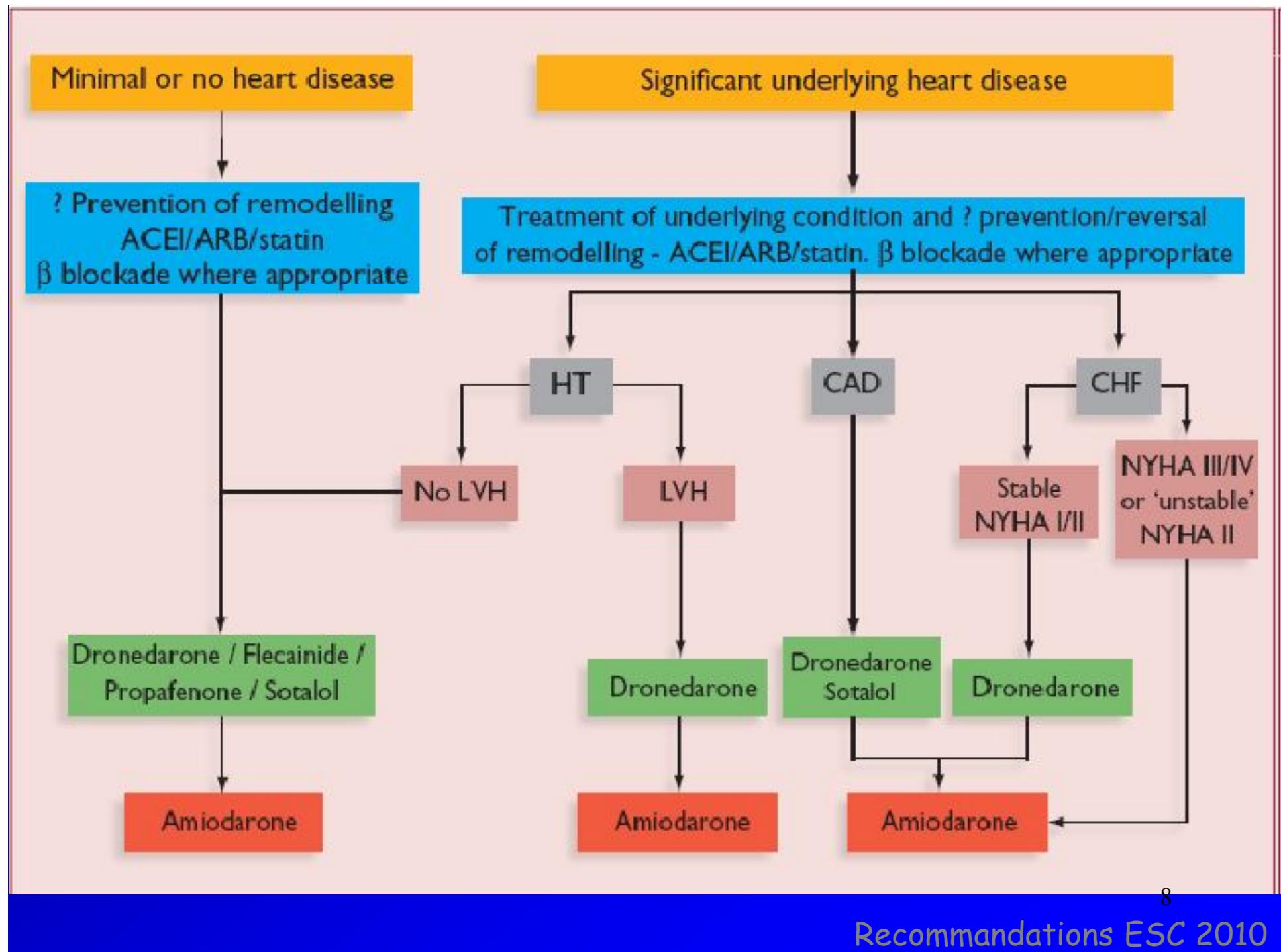
# **Guidelines for the management of atrial fibrillation**



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

*The European Society of Cardiology 2010*

**Le Traitement Antiarythmique  
de la Fibrillation Atriale**



# Thérapie adjuvante en prévention des récidives de FA

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| ACEIs and ARBs should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.                           | IIa                | A                  | 145–149           |
| ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.          | IIa                | B                  | 147, 150, 151     |
| Statins should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions. | IIa                | B                  | 161, 162          |
| Statins may be considered for prevention of new-onset AF in patients with underlying heart disease, particularly heart failure.                            | IIb                | B                  | 164, 165          |
| Upstream therapies with ACEIs, ARBs, and statins are not recommended for primary prevention of AF in patients without cardiovascular disease.              | III                | C                  |                   |

Nouvelles places des IEC / ARA<sub>2</sub> et statines

Niveaux de preuves A et B  
Recommandations ESC 2010

|   |   |        |
|---|---|--------|
| The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:   |   |        |
| • amiodarone  | I | A      |
| • dronedarone   | I | A      |
| • flecainide  | I | A      |
| • propafenone   | I | A      |
| • d,l-sotalol   | I | A      |
| Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C). | I | A<br>C |
| In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.   | I | B      |
| In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.   | I | A      |
| β-Blockers are recommended for prevention of adrenergic AF.   | I | C      |

## Choix du traitement anti-arythmique

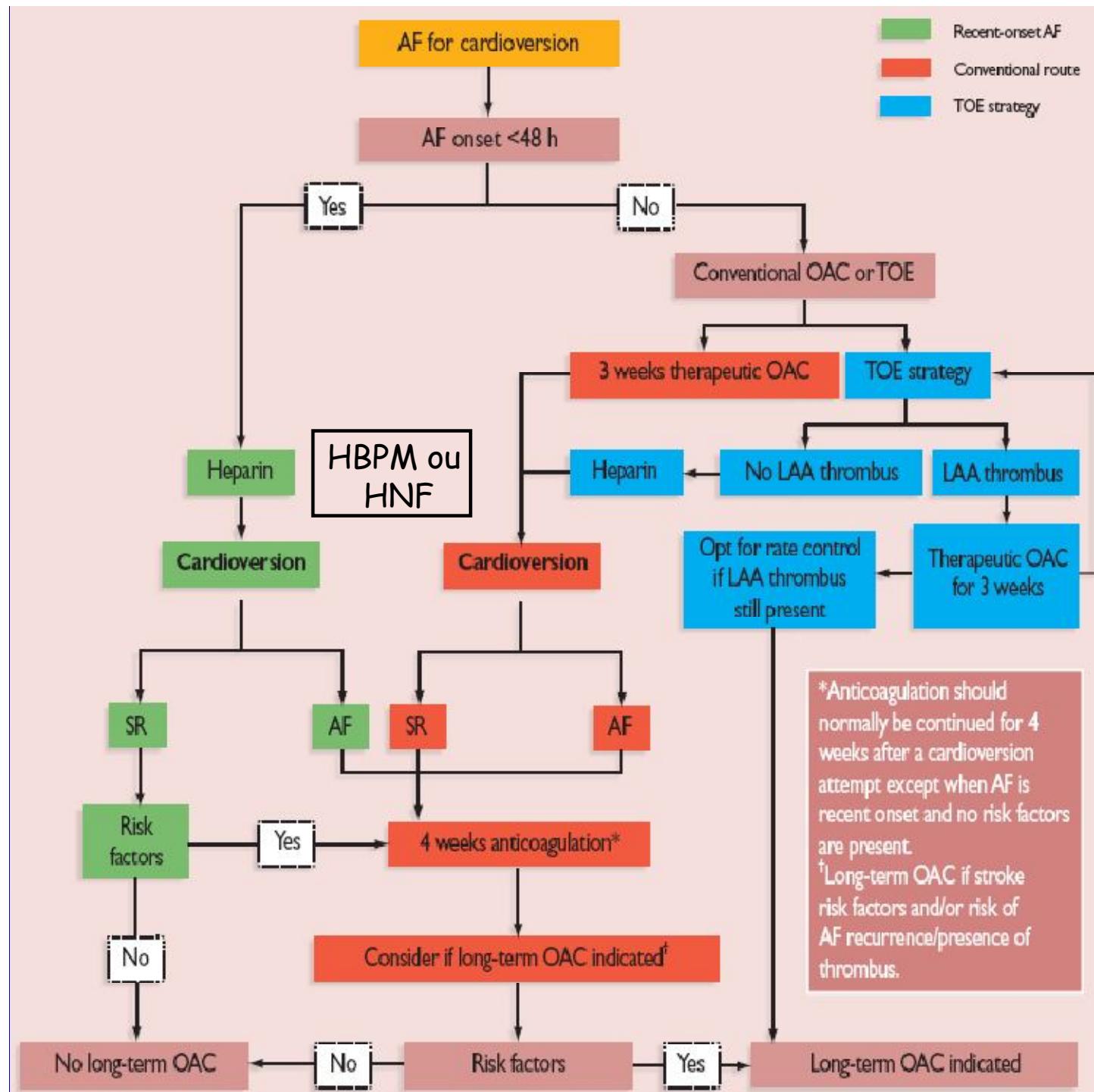
|  |     |   |        |
|--|-----|---|--------|
| If one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level, the use of another antiarrhythmic drug should be considered. | IIa | C |        |
| Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.         | IIa | B | 95, 99 |
| β-blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.   | IIa | C |        |

*Patients with left ventricular hypertrophy: flecaine, propafenone ( $LVWT < 14 \text{ mm}$ ); dronedarone or amiodarone ( $LVWT > 14 \text{ mm}$ )*

*Patients with coronary artery disease: sotalol or Dronedarone (first line), amiodarone (last resort)*

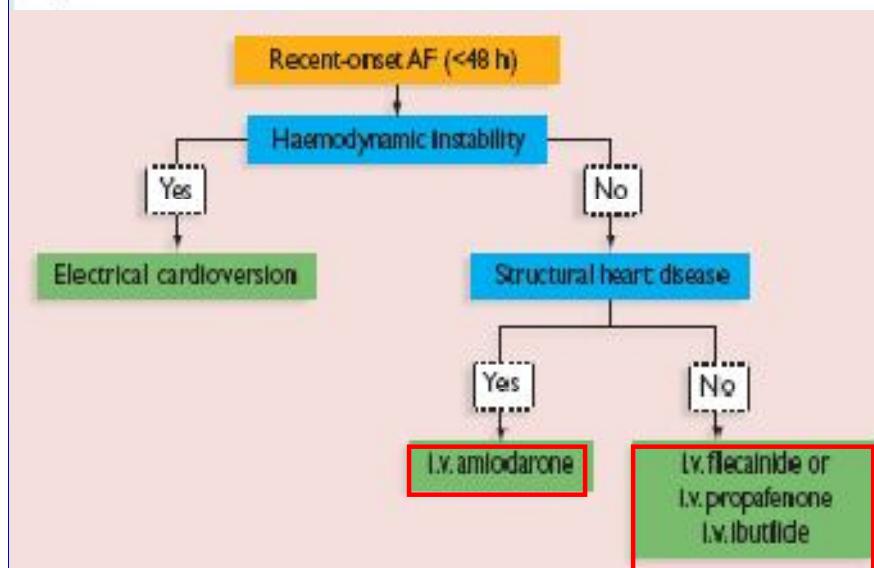
*Patients with heart failure: dronedarone and amiodarone in NYHA I-II, amiodarone only in NYHA III-IV<sup>10</sup>*

## Anticoagulation Péri-cardioversion



**Table 12** 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   | Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.   |
| Flecainide  | 2 mg/kg i.v. over 10 min.<br>or<br>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.               |
| Ibutilide   | 1 mg i.v. over 10 min                              | 1 mg i.v. 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.<br>or<br>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 i.v. over 10 min after 15 min rest | So far only evaluated in clinical trials; recently approved. <sup>68–70</sup>  |



## Cardioversion pharmacologique

# La place de la Dronédarone

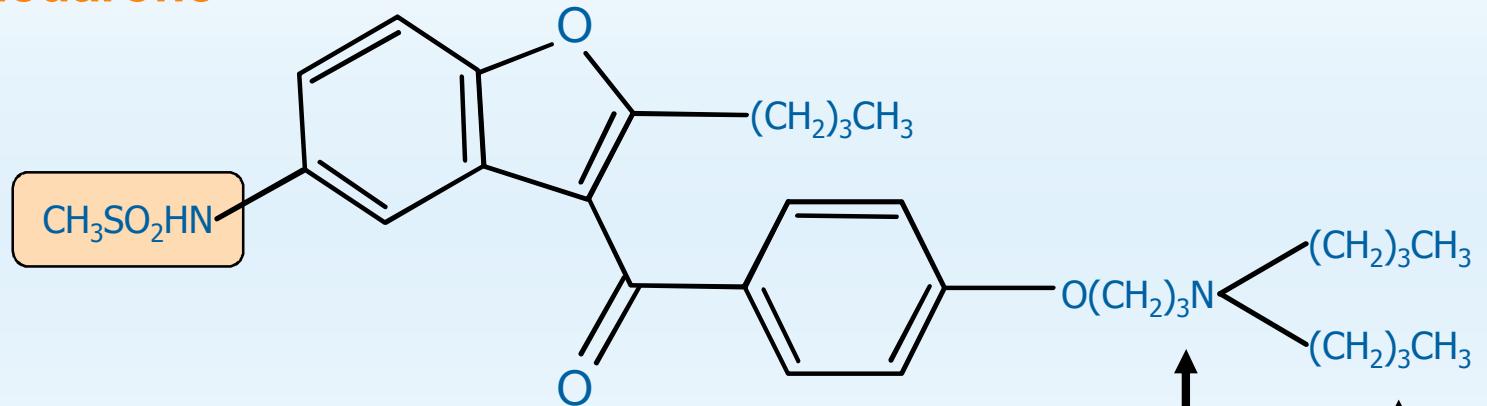
## Données de la littérature

- Dronedarone is a multichannel blocker that inhibits the sodium, potassium, and calcium channels, and has non-competitive antiadrenergic activity
- Dronedarone was shown in two large pivotal trials to be superior to placebo in maintaining sinus rhythm in patients with recurrent AF.
- In the DIONYSOS study [...] in 504 patients with persistent AF, dronedarone was less efficacious but also less toxic than amiodarone.
- The ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA) trial in patients in sinus rhythm and advanced heart failure (NYHA III-IV + LV dysfunction) was stopped prematurely due to increased mortality with dronedarone (**Increased HF**)

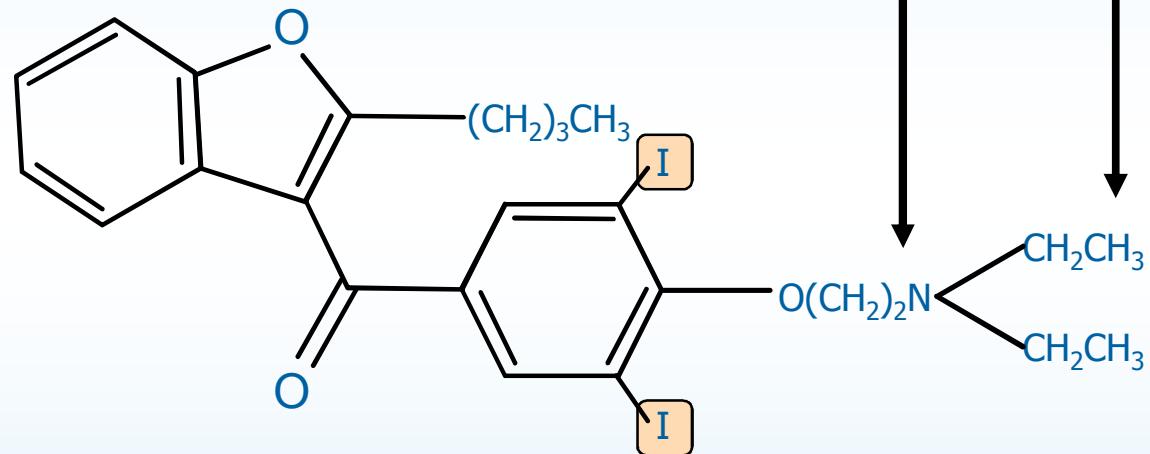
Contre-indication en cas d'IC NYHA III-IV, dysfonction systolique VG

# Principales différences structurelles entre la dronédarone et l'amiodarone

Dronédarone



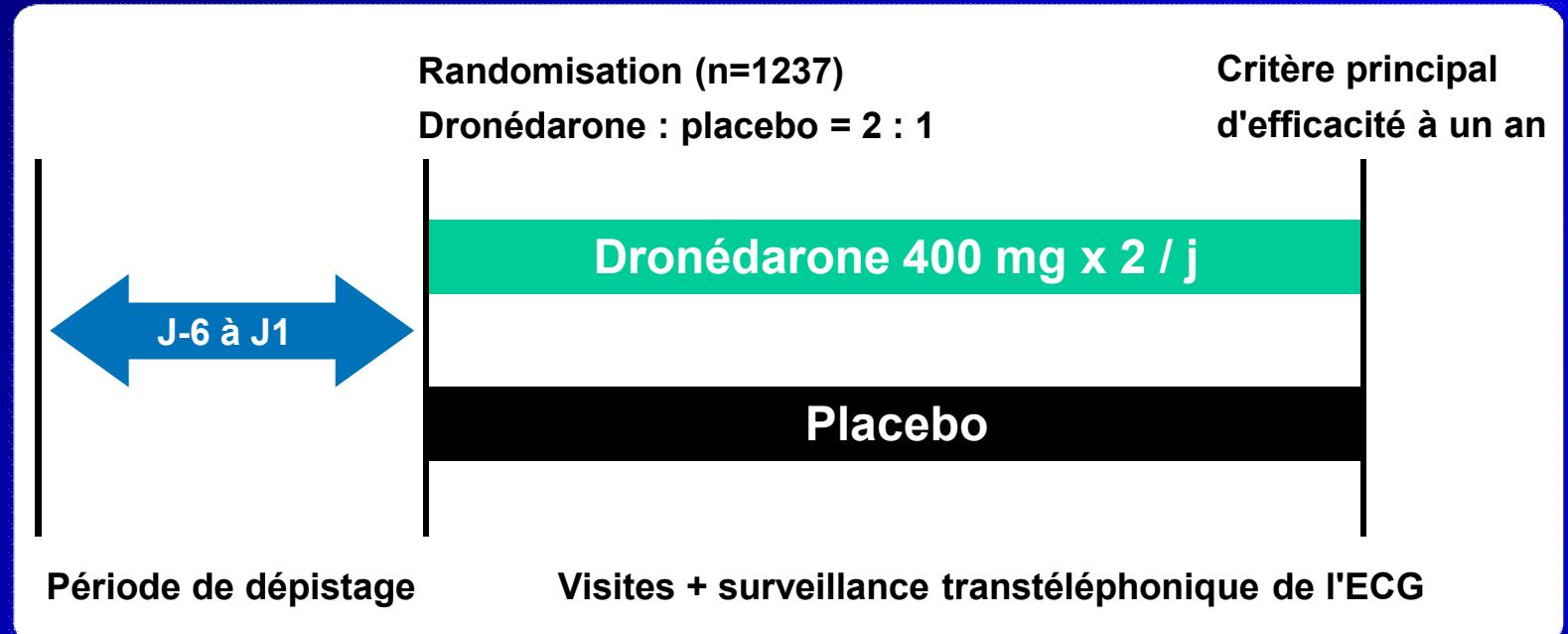
Amiodarone



14

# Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

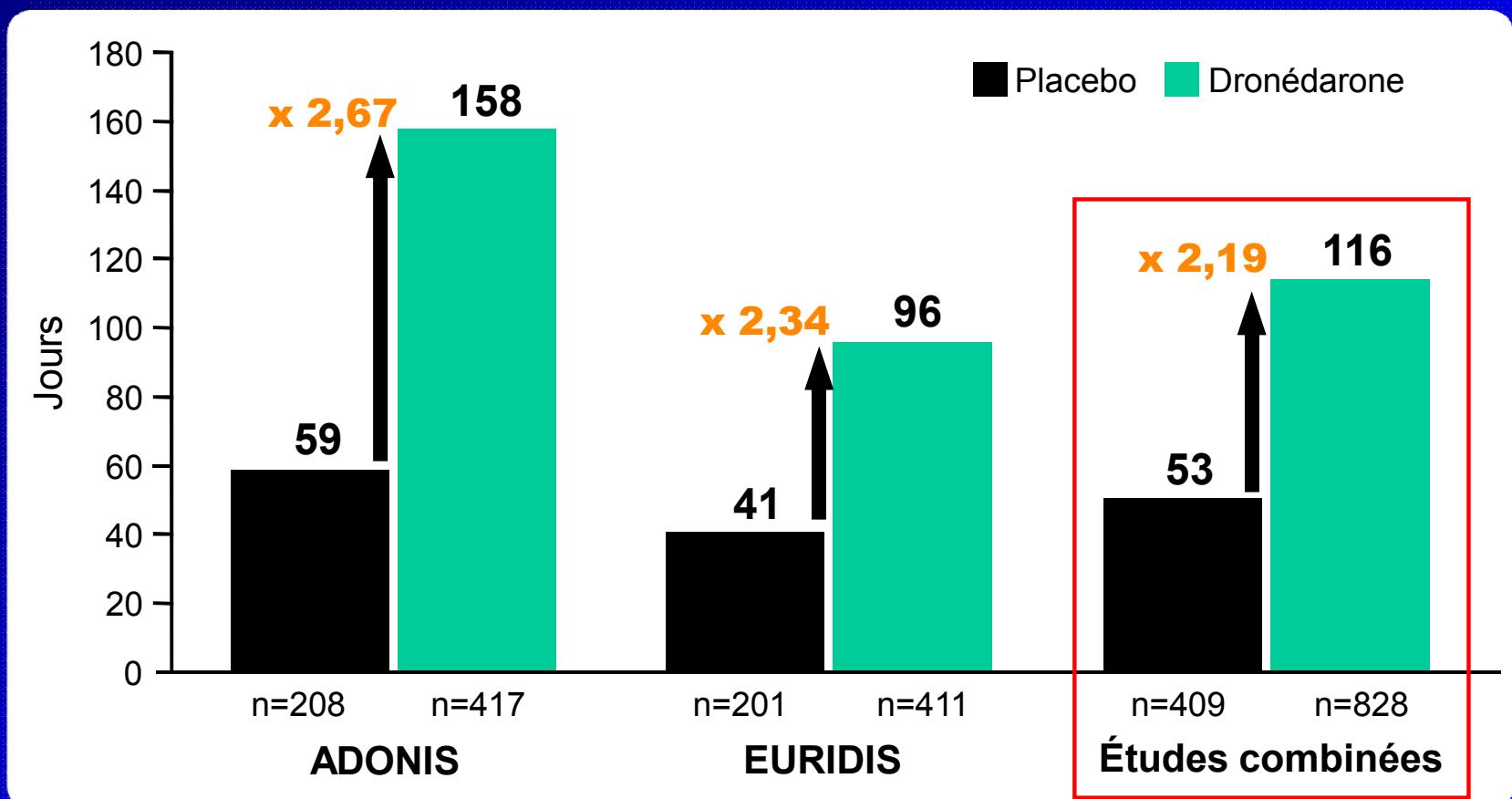
N Engl J Med 2007;357:987-99.



**Critère principal:** délai d'apparition de récidive de FA / Flutter

# Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

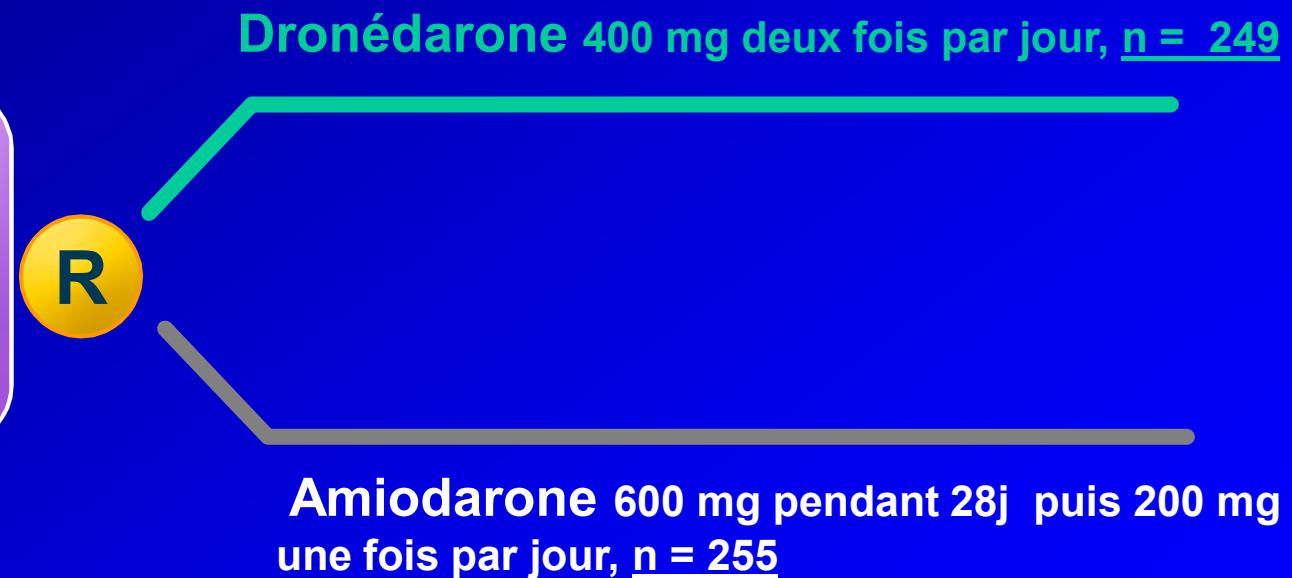
N Engl J Med 2007;357:987-99.



# A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study

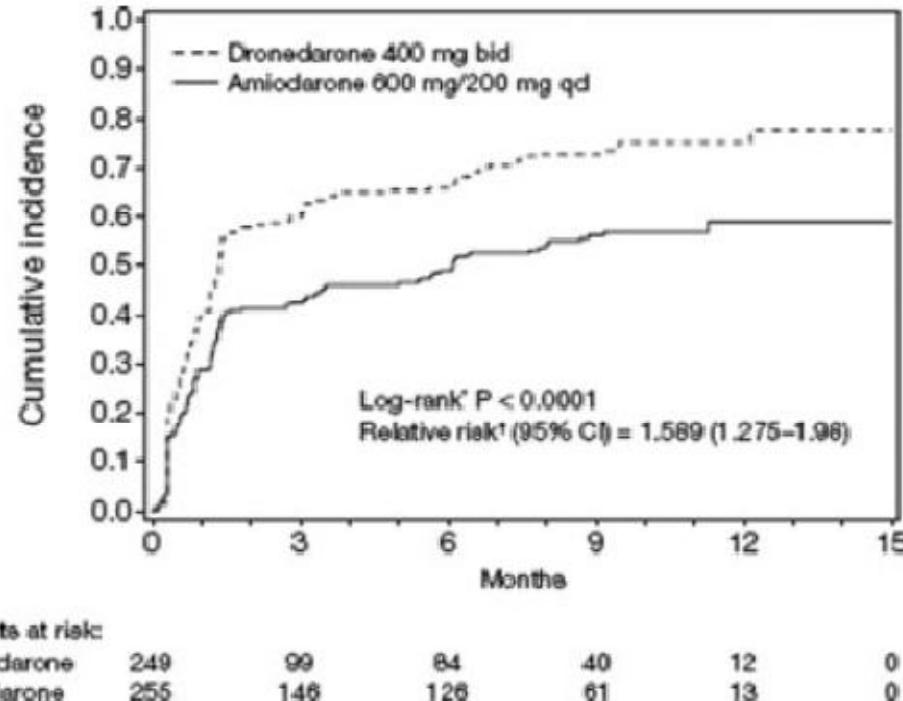
Le Heuzey J Cardiovasc Electrophysiol 2010, Vol, 1-9

504 patients  
présentant une FA  
persistante  
éligibles pour une  
cardioversion  
électrique



# A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study

Le Heuzey J Cardiovasc Electrophysiol 2010, Vol. 1-9



**Figure 3.** Kaplan-Meier plot of cumulative incidence of recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy, according to investigator's judgment, in patients receiving dronedarone (400 mg bid) or amiodarone (600 mg qd for 28 days and 200 mg qd thereafter) for at least 6 months. Log-rank test is based on entire curve. \*Pairwise comparison.

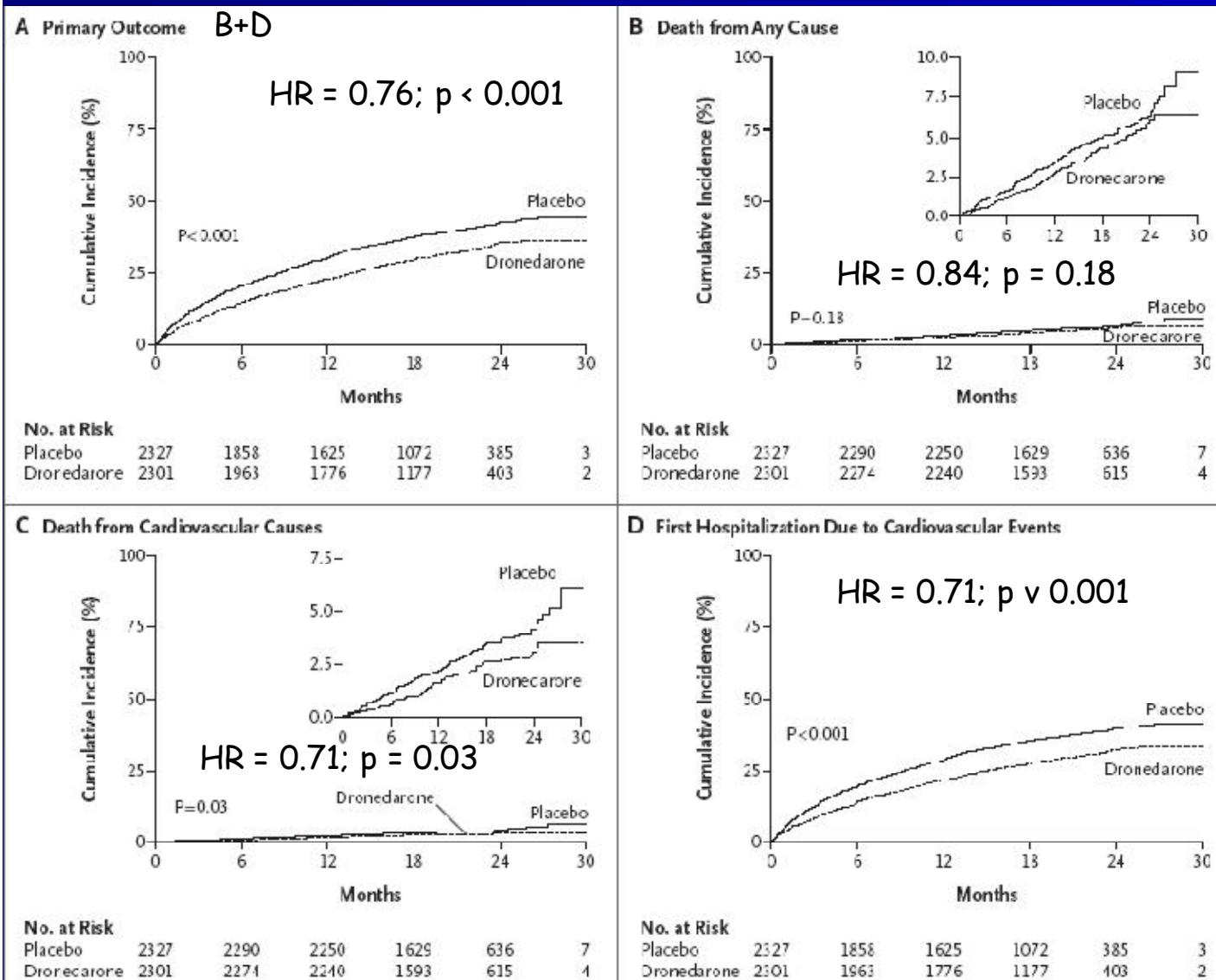
TABLE 2  
Composition of the Primary Endpoint (Crude Rates)

|   | Dronedarone<br>400 mg<br>bid (n = 249) | Amiodarone<br>600 mg/<br>200 mg once<br>qd (n = 255) |
|---|--|--|
| Number of patients with endpoint (%)  | 184 (73.9)                             | 141 (55.3)   |
| AF recurrence <sup>†</sup> , n (%)  | 158 (63.5)                             | 107 (42.0)   |
| Documented AF after conversion  | 91 (36.5)                              | 62 (24.3)  |
| Unsuccessful electrical cardioversion   | 29 (11.6)                              | 16 (6.3)   |
| No spontaneous conversion and no electrical cardioversion on day 10 to day 28 | 38 (15.3)                              | 29 (11.4)  |
| Premature study drug discontinuation, n (%)                                   | 26 (10.4)                              | 34 (13.3)  |
| Lack of efficacy  | 1 (0.4)                                | 0  |
| Intolerance   | 25 (10.0)                              | 34 (13.3)  |

Primary endpoint is defined by AF recurrence or premature study drug discontinuation, whichever comes first.

# Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

N Engl J Med 2009;360:668-78.



4628 patients

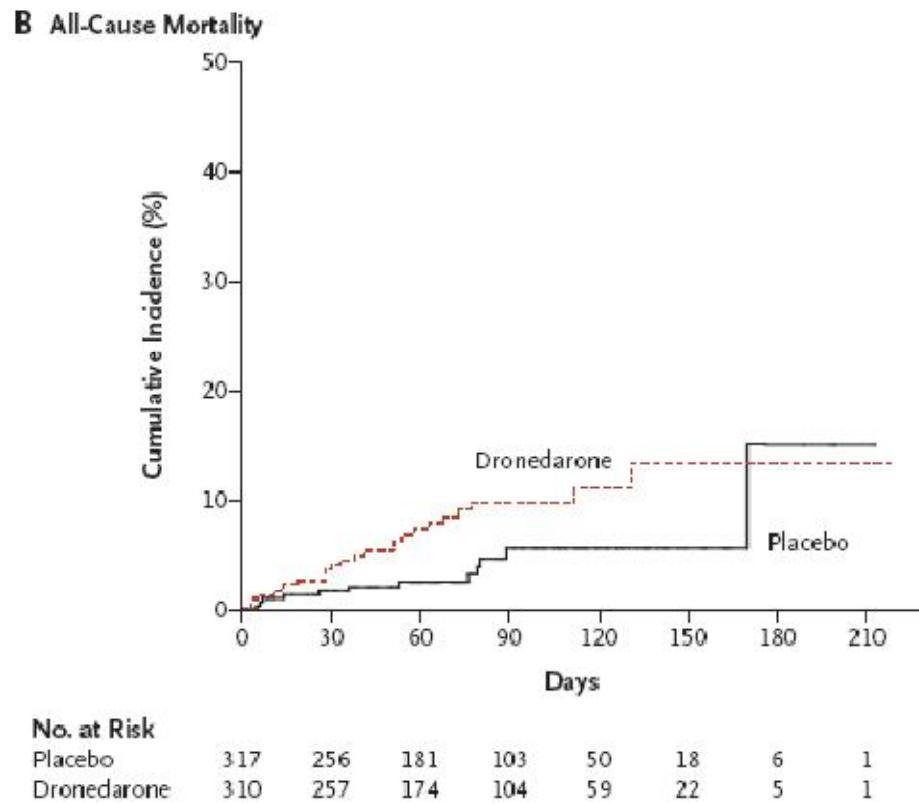
Placebo, n = 2327  
Dronedarone,  
n = 2301

Figure 2. Kaplan-Meier Cumulative Incidences of the Primary and Secondary Outcomes.

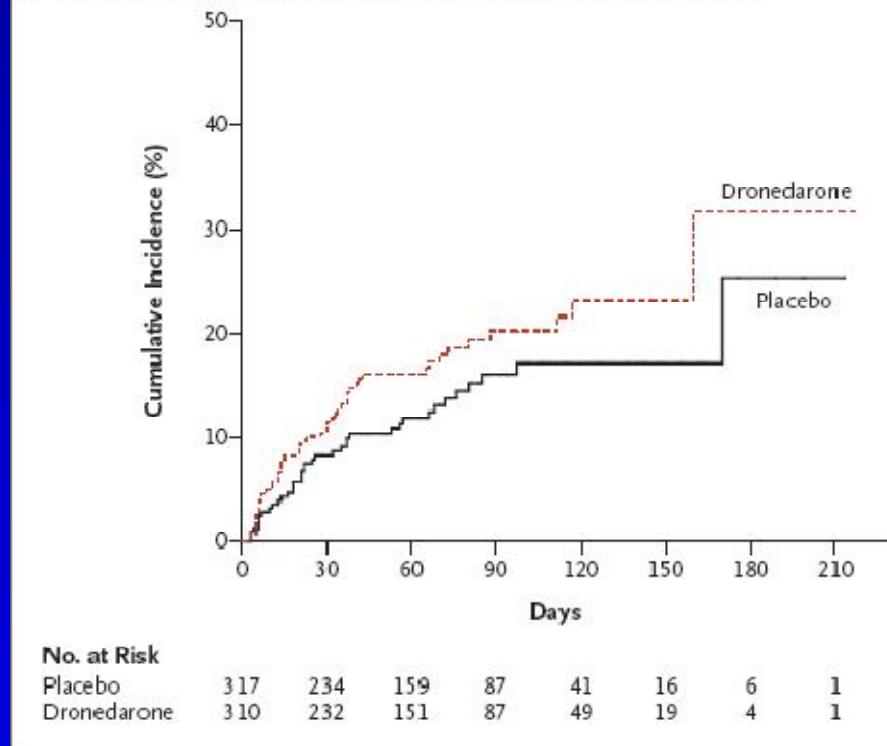
# Increased Mortality after Dronedarone Therapy for Severe Heart Failure

N Engl J Med 2008;358:2678-87.

- NYHA III-IV le mois précédent
- FeVG < 35 %. Suivi 12 mois
- Réduction des hospitalisations pour IC ?
- Réduction de la mortalité par arythmie Ventriculaire ?



**A All-Cause Mortality or Hospitalization for Worsening Heart Failure**



During a median follow-up of 2 months, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07 to 4.25; P = 0.03)

20

# La place de la Dronédarone

Janvier 2011

- Cas rapportés d'hépatite médicamenteuse chez des patients traités par la dronédarone MULTAQ™ (2 transplantations hépatiques)
- Suivi biologique hépatique ASAT/ALAT avant traitement puis tous les mois pendant 6 mois, 9 et 12 mois et régulièrement par la suite
- Arrêt si cytolyse hépatique > 3 N