

New antiarrhythmic drugs for prevention and treatment of atrial fibrillation: do they represent a real progress?

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Atrial fibrillation is the most common sustained arrhythmia exacting a substantial cost in morbidity and mortality. Despite new insights into the pathophysiological mechanism of atrial fibrillation (AF) and the development of new antiarrhythmic drugs, as well as more sophisticated ablative techniques, the management of this rhythm disturbance remains problematic.

Rhythm vs Rate control

A series of landmark trials have investigated the two treatment strategies, rhythm and rate control, in AF patients:

PIAF (Pharmacological Intervention in AF)

STAF (Strategies of Treatment of AF)

RACE (Rate Control vs Electrical conversion)

AFFIRM (AF Follow-up of Rhythm Management)

HOT-CAFE (How to treat Chronic AF)

Rhythm vs Rate Control

- The results from these trials showed that the strategy of rate control is at least equivalent with the rhythm control strategy
- These trials have also indicated the necessity of continuing antithrombotic treatment, with both strategies, even when sinus rhythm is maintained

Rhythm vs Rate control

These clinical trials have important limitations and are not representative of the AF population as a whole. Therefore, their findings are not applicable to all groups of AF patients.

Rhythm vs Rate control

Patients in Sinus Rhythm

	Rhythm Control group	Rate Control group
PIAF	56%	10%
STAF	23%	9%
RACE	39%	10%
AFFIRM	63%	35%
HOT- CAFE	63,5%	-

Rhythm vs Rate control

Failure to maintain sinus rhythm in a large number of patients in these trials, may represent:

1. An enrollment bias at least in the trials with the lower incidence of normal SR.
2. The need for more effective and safer "antiarrhythmic" therapies for the long-term maintenance of SR.

Antiarrhythmic Drugs for AF

- Following the results of the CAST study:
 - *Which showed that class I antiarrhythmic drugs increase the incidence of death in survivors of MI.*
- and after the results of the SWORD study:
 - *Where d-sotalol, a pure class III agent, increased mortality, most likely related to proarrhythmic effect.*

Investigation focused on drugs with multifactorial modes of action.

Antiarrhythmic Drugs for AF

Therefore, the research for class III agents has continued, and pure class III drugs like **dofetilide** and **ibutilide** have been investigated in clinical trials and have received approval for clinical use.

Investigational antiarrhythmic agents for treatment of AF

- AA Drugs with traditional antiarrhythmic mechanism of action
- AA Drugs with novel mechanisms of action

Investigational antiarrhythmic agents for treatment of AF

AA Drugs with traditional antiarrhythmic mechanism of action

- Blockers of multiple ion channels (Class III)
 - e.g. azimilide
 - tedisamil
 - ersentilide
 - trecetilide
- Dronedarone (Class I-IV)

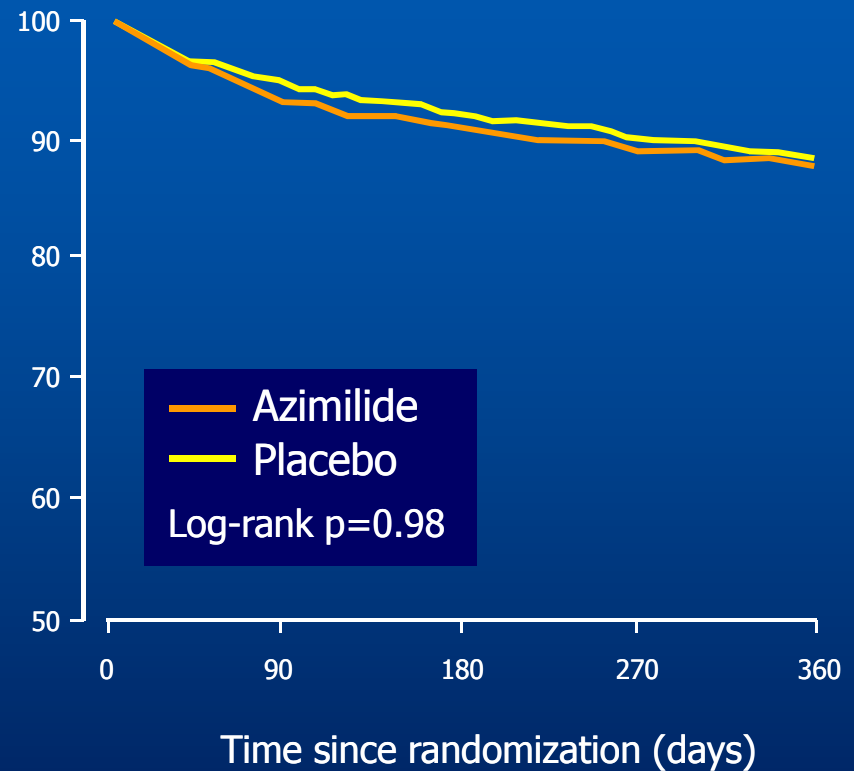
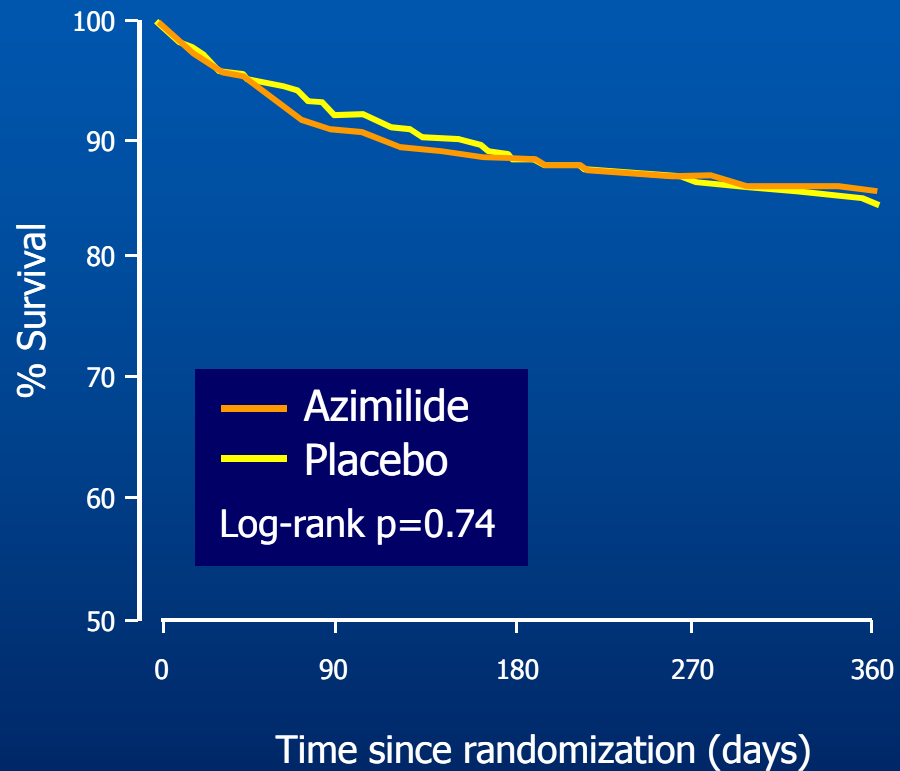
Azimilide

Properties of Azimilide

- Blocks both I_{kr} and I_{ks} channels
- Oral bioavailability greater than 85%
- Prolongs the myocyte action potential, independently of heart rate. Does not have reverse use dependence.
- No dose adjustments required for:
 - Renal or hepatic impairment
 - Use with warfarin or digoxin

Survival Curves All-Cause Mortality

ALIVE

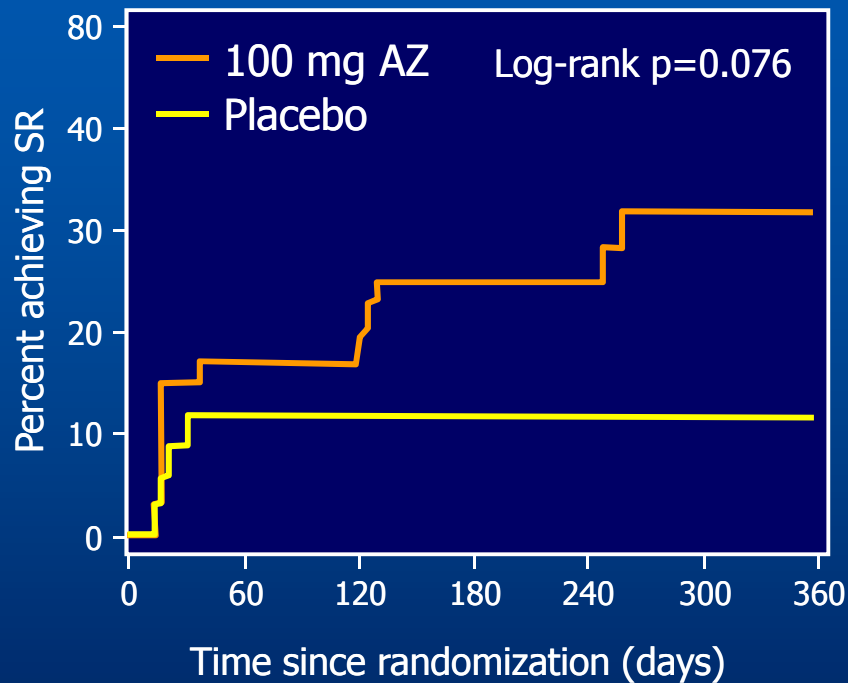


Patients at risk

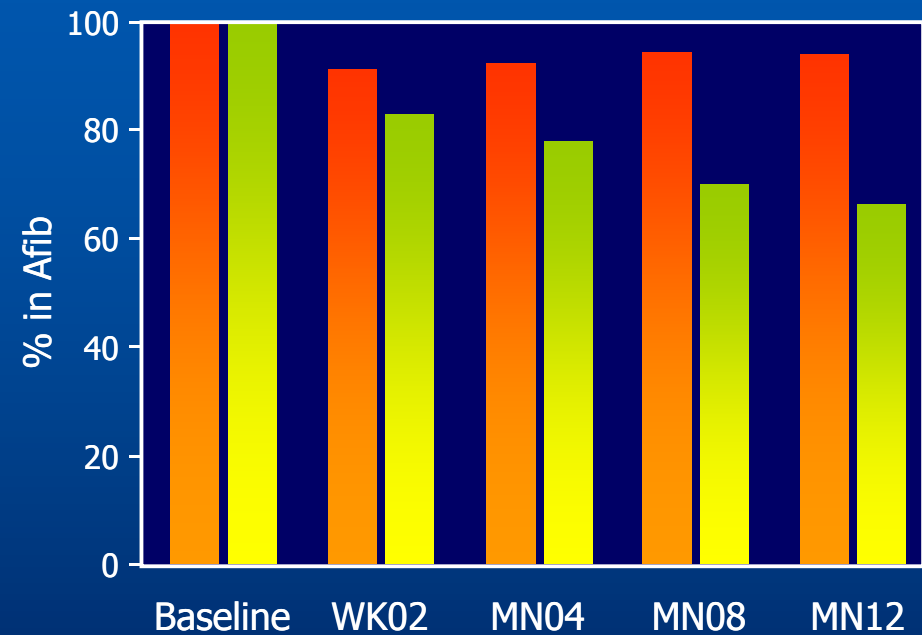
Azimilide	622	564	548	541	519	1691	1578	1542	1510	1440
Placebo	642	592	568	554	530	1690	1601	1557	1526	1450

Azimilide in patients with AF

ALIVE



Spontaneous conversion to SR among patients in AF at baseline



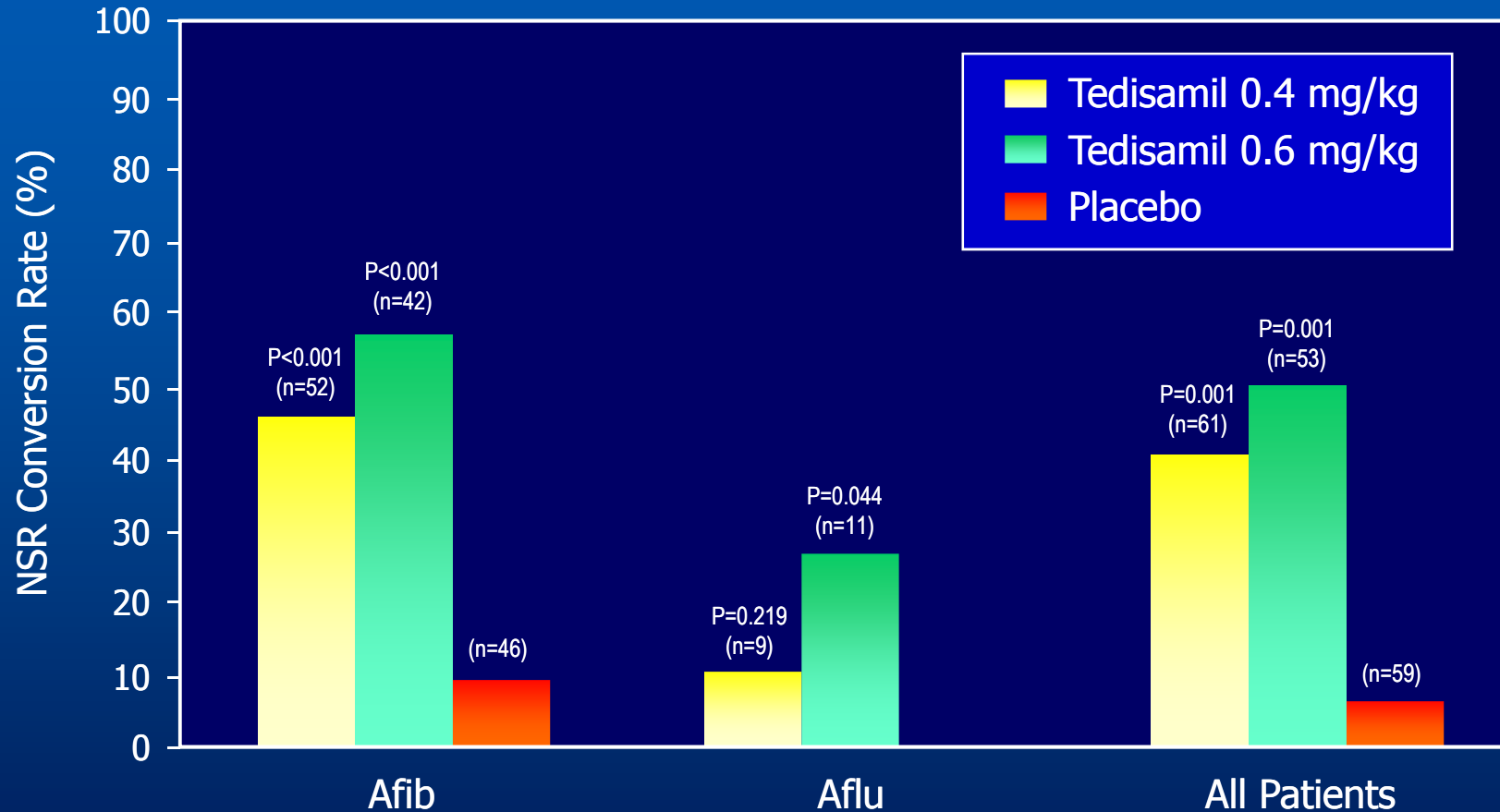
Prevalence of AF during the trial among patients with AF at baseline

Tedisamil

Properties of Tedisamil

- Blocks multiple membrane ion channels and slows sinus rate.
 - Transient outward current I_{to}
 - Delayed potassium rectifier currents I_{kr} , I_{ks} and I_{kur}
- Prolongs both atrial and ventricular action potential duration
- The drug is excreted via the kidney
- Half-life 8-13 hs
- Possesses antianginal and anti-ischemic properties
- I.V. preparation

Tedisamil for Conversion of AF



Cumulative incidence of drug-associated conversion to normal sinus rhythm (NSR) within the first 2.5 h after drug administration in patients with atrial fibrillation (Afib) or atrial flutter (Aflu) and in the entire patient population. Numbers in parentheses indicate patients treated.

S.H. Hohnloser, JACC 2004

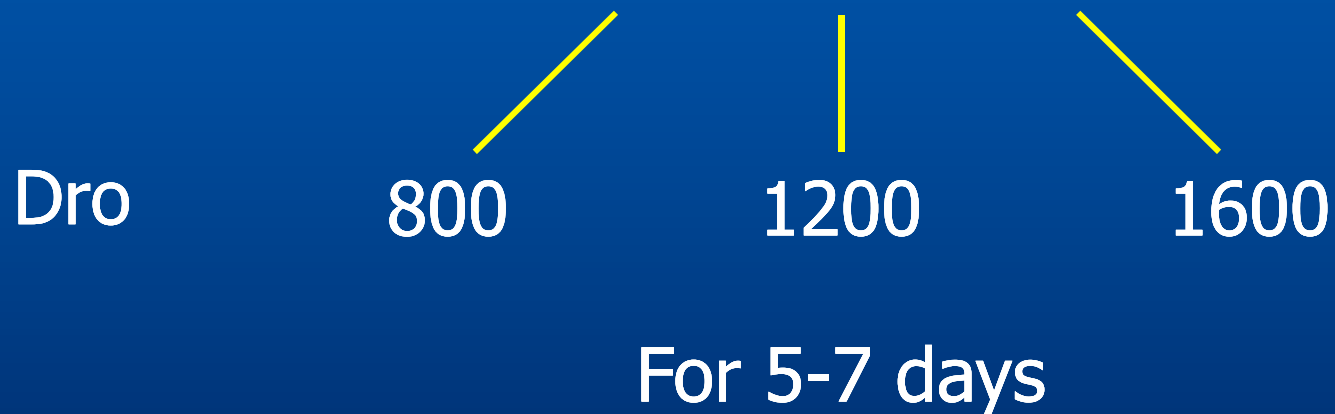
Dronedarone

Phase III Clinical Trials

- ANDROMEDA:** Mortality trial, in a high-risk population (LVEF <35%).
- DAFNE:** Dose-ranging trial, assessing sinus rhythm maintenance in AF patients undergoing cardioversion.
- EURIDIS-ADONIS:** Confirmatory trials of assessing the efficacy and safety of dronedarone for sinus rhythm maintenance in patients with atrial fibrillation.
- ERATO:** A rate control trial in patients with permanent atrial fibrillation.

DAFNE Trial

Patients with persistent AF
Anticoagulation for 3 weeks

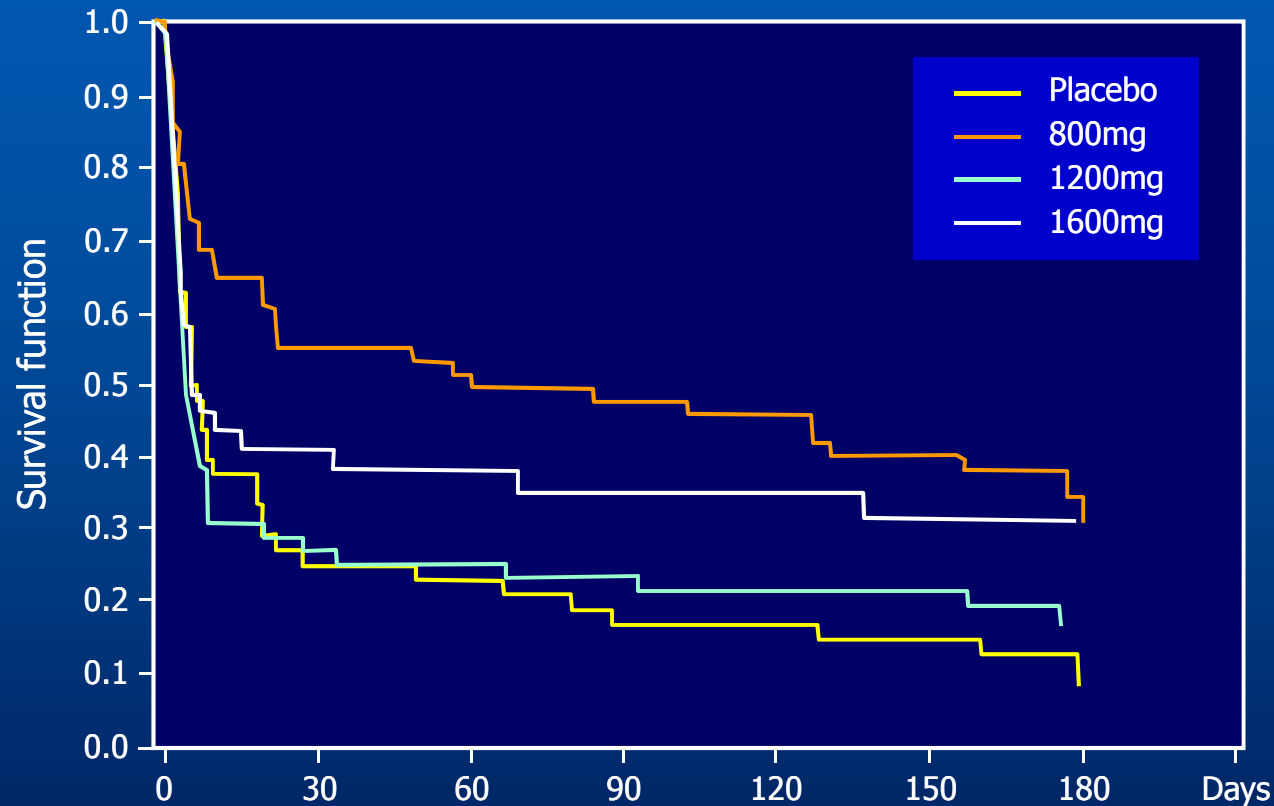


If SR was not restored → ECV

Follow-up on treatment: 6 months

DAFNE

Dronedarone for prevention of atrial fibrillation: A dose – ranging study



	0	30	60	90	120	150	180
Placebo n exp.=	48	12	11	8	8	7	5
800mg n exp.=	54	29	26	25	24	21	18
1200mg n exp.=	54	14	13	12	11	11	9
1600mg n exp.=	43	15	12	11	11	9	8

The difference in time to atrial fibrillation relapse between the dronedarone 800mg group and the placebo group was significant ($P=0.001$).

DAFNE trial

Conclusion

Dronedarone, at a 800mg daily dose, appears to be effective and safe for the prevention of AF relapses after cardioversion. The absence of thyroid side effects and of proarrhythmia are important features of the drug.

Investigational antiarrhythmic agents for treatment of AF

AA Drugs with novel mechanisms of action

- Atrial ion channels selective agents (Ikur blockers)
e.g. RSD 1235
AVE 1231
- Selective adenosine A₁-blockers
e.g. tecadenoson
- Stretch receptor antagonists
GsMtx4
- Serotonin receptor antagonists
piboserod
- GAP Junction Modulators
e.g. ZP 123
AAP 10
- RAAS Antagonists
ACE-1
ARBs

Properties of RSD 1235

- A frequency dependent Na⁺ channel blocker and atrial selective K⁺ channel blocker.
- Prolongs selectively the atrial refractory period.
- Does not appear to affect ventricular refractoriness or QT interval.
- I.V. RSD 1235 appears to be efficacious and safe for recent onset AF conversion to sinus rhythm.

Roy et al JACC 2004;44:2355-61

Conclusions

- Currently, rate control and anticoagulation is the treatment of choice in elderly, minimally symptomatic patients.
- For the younger patients without risk factors for stroke, the highly symptomatic patients or the patients with paroxysmal AF without structural heart disease, rhythm control might be preferable. Carefully designed trials are required to define the role of pharmacological rhythm control in this AF population.
- The promising new antiarrhythmic agents that are undergoing investigation, offer a prospect of an effective and safer antiarrhythmic therapy for the AF patients.
To testify the above more clinical trials are needed.