Pharmacological treatment of atrial fibrillation: current status and future prospects

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Advantages of Sinus Rhythm

- Improvement in hemodynamics, exercise tolerance, quality of life
- Reduction of thromboembolic events
- Avoidance of complications due to anticoagulant therapy
- Better survival

AF mechanisms

Trigger

Premature atrial complex

Substrate

Anatomical:
Atrial dilatation,
Fibrosis,
Hypertrophy

Electrophysiological:
ERP shortening,
ERP dispersion,
Lack of rate-adaptation of ERP, delay or block of intraatrial conduction.

Coumel Triangle

Autonomic nervous system

Vagal (bradycardia)
Adrenergic

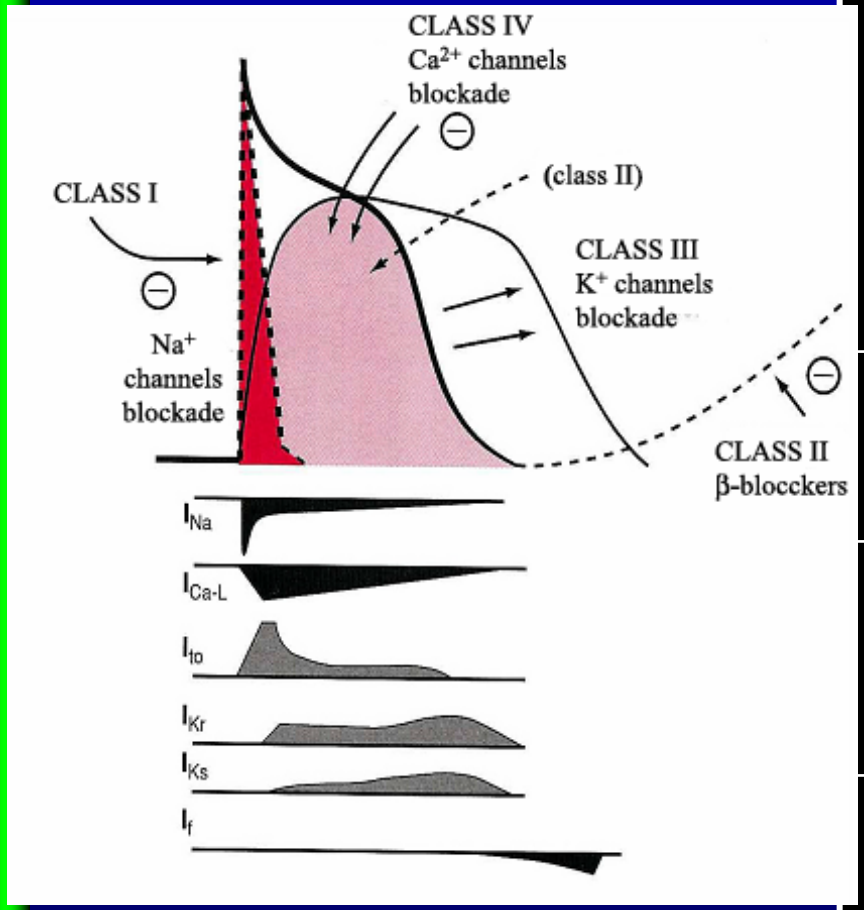
Therapeutic strategies

Antiarrhythmic drugs

Substrate altering drugs

Ablative therapy

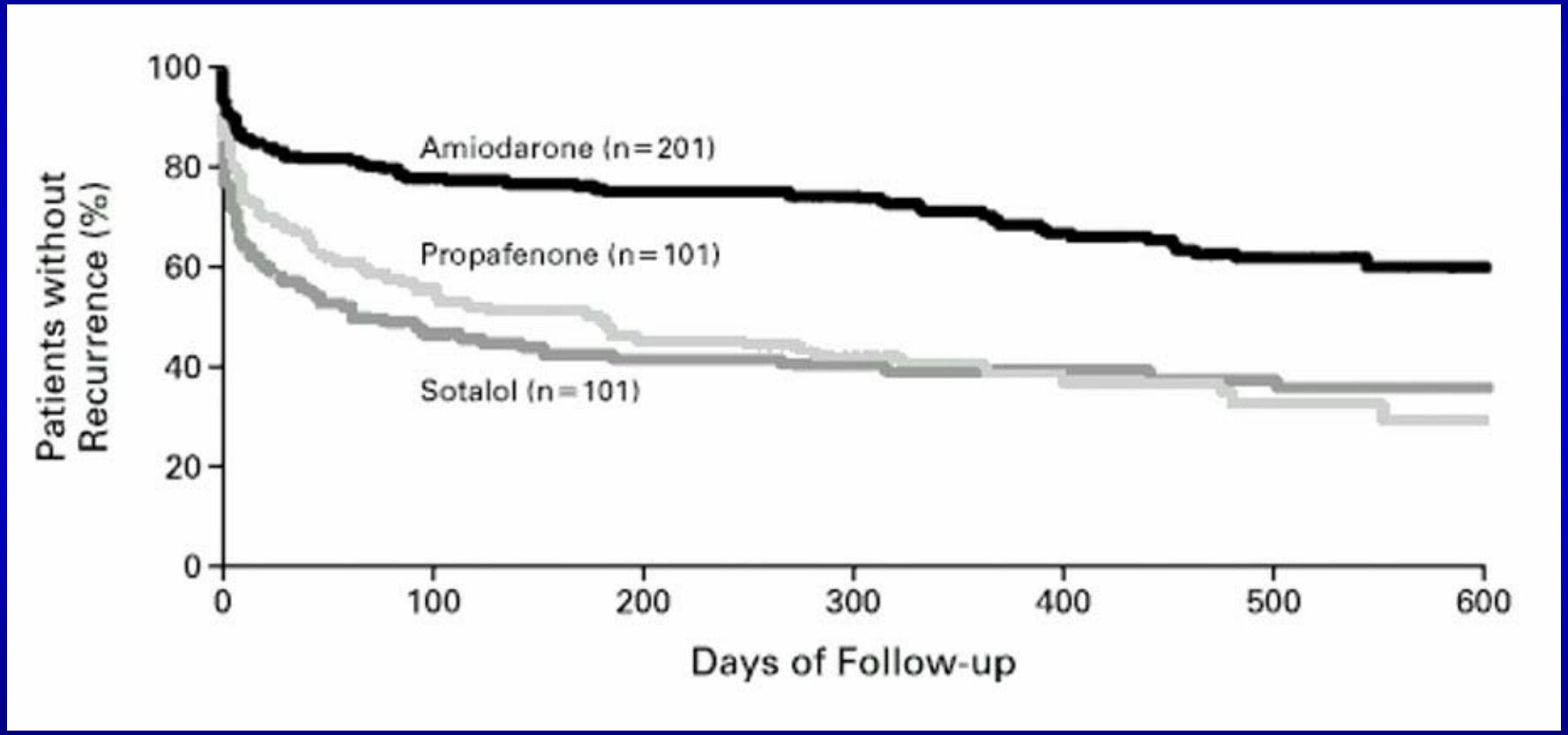
Antiarrhythmic drugs



Vaughan Williams Classification

Class		Action		Drugs
I	IA	Sodium Channel Blockad	Prolong repolarization	Quinidine Procainamide Disopyramide
	IB		Shorten repolarization	Lidocaine Mexiletine Tocainide Phenytoin
	IC		Little effect on repolarization	Encainide Flecainide Propafenone moricizine(?)
II		Beta-Adrenergic Blockade		Propanolol Esmolol Acebutolol *l*-sotalol
III		Prolong Repolarization (Potassium Channel Blockade; Other)		Ibutilide Dofetilide Sotalol (*d,l*) Amiodarone Bretylium
IV		Calcium Channel Blockade		Verapamil Diltiazem Bepridil
Miscellaneous		Miscellaneous Actions		Adenosine Digitalis Magnesium

Long term efficacy of Amiodarone to maintain SR: CTAF study



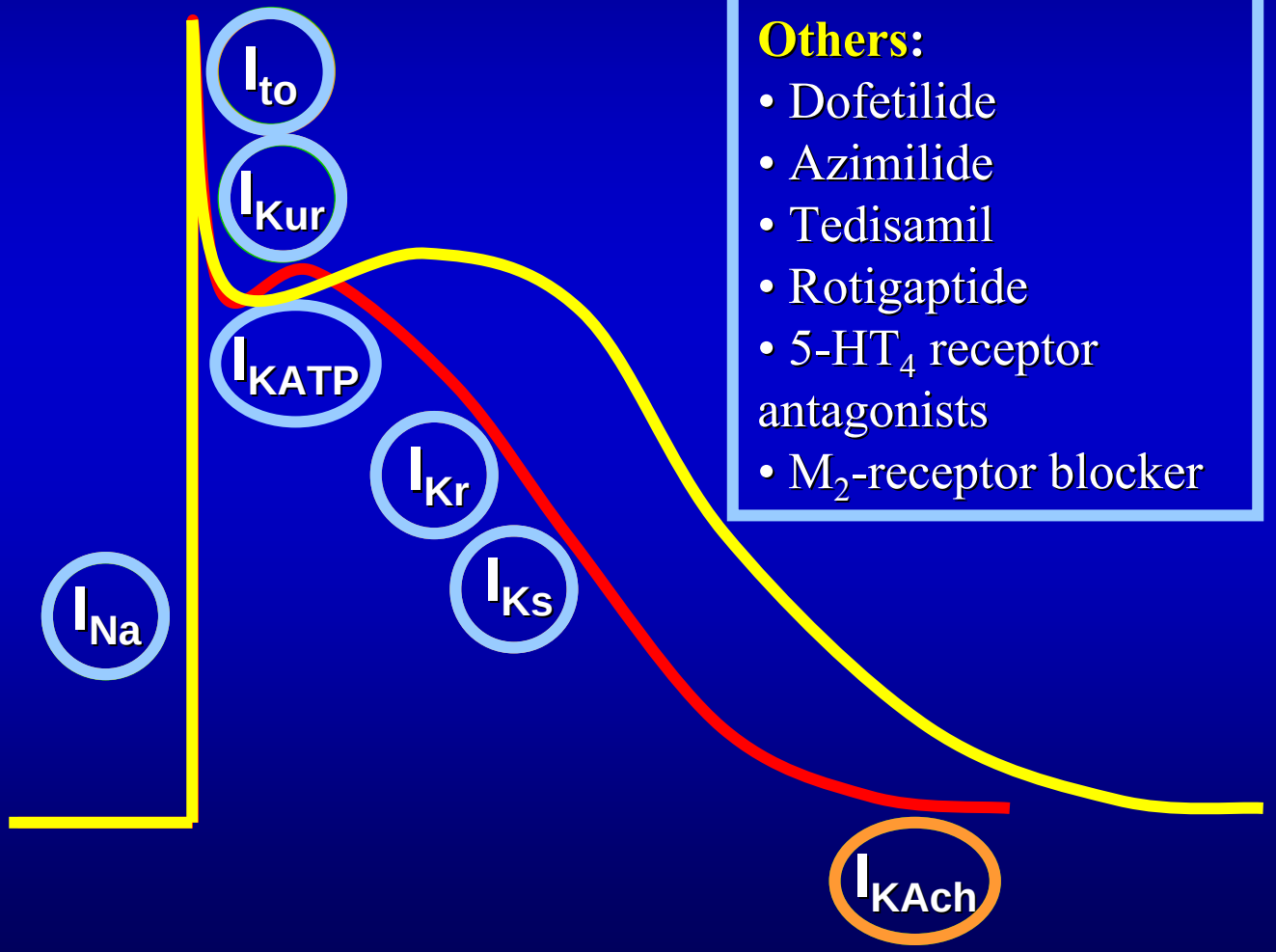
Roy D et al. NEJM 2000; 342:913-920

New antiarrhythmic drugs

New antiarrhythmic drugs

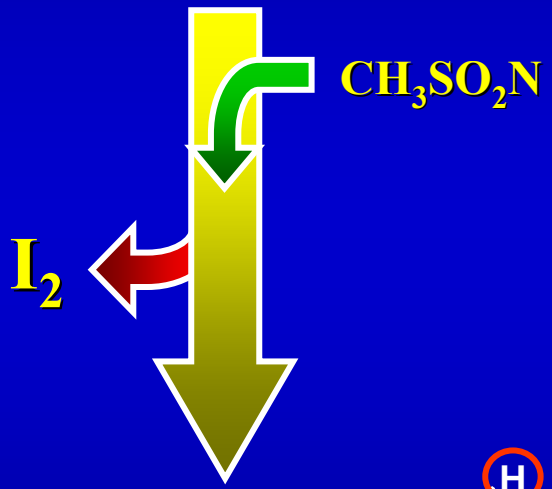
Atrial selective drugs:
- Vernakalant
- AVE0118
- AZD7009

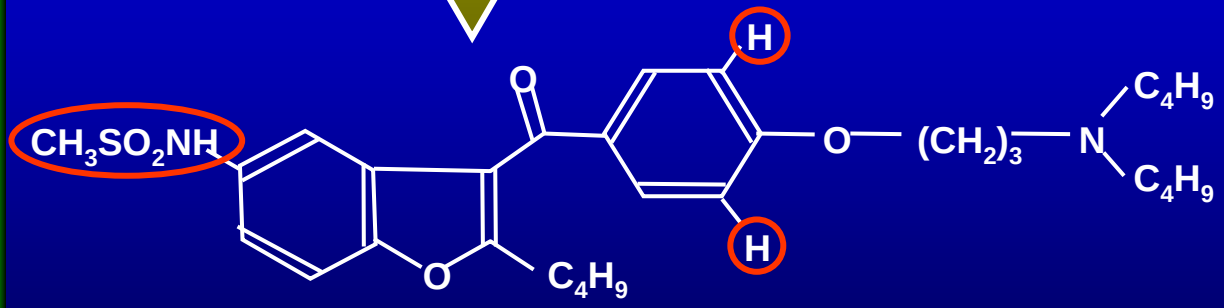
Amiodarone congeners:
- Dronedarone
- SSR149744C
- ATI-2042



Others:
- Dofetilide
- Azimilide
- Tedisamil
- Rotigaptide
- 5-HT_4 receptor antagonists
- M_2-receptor blocker

Amiodarone

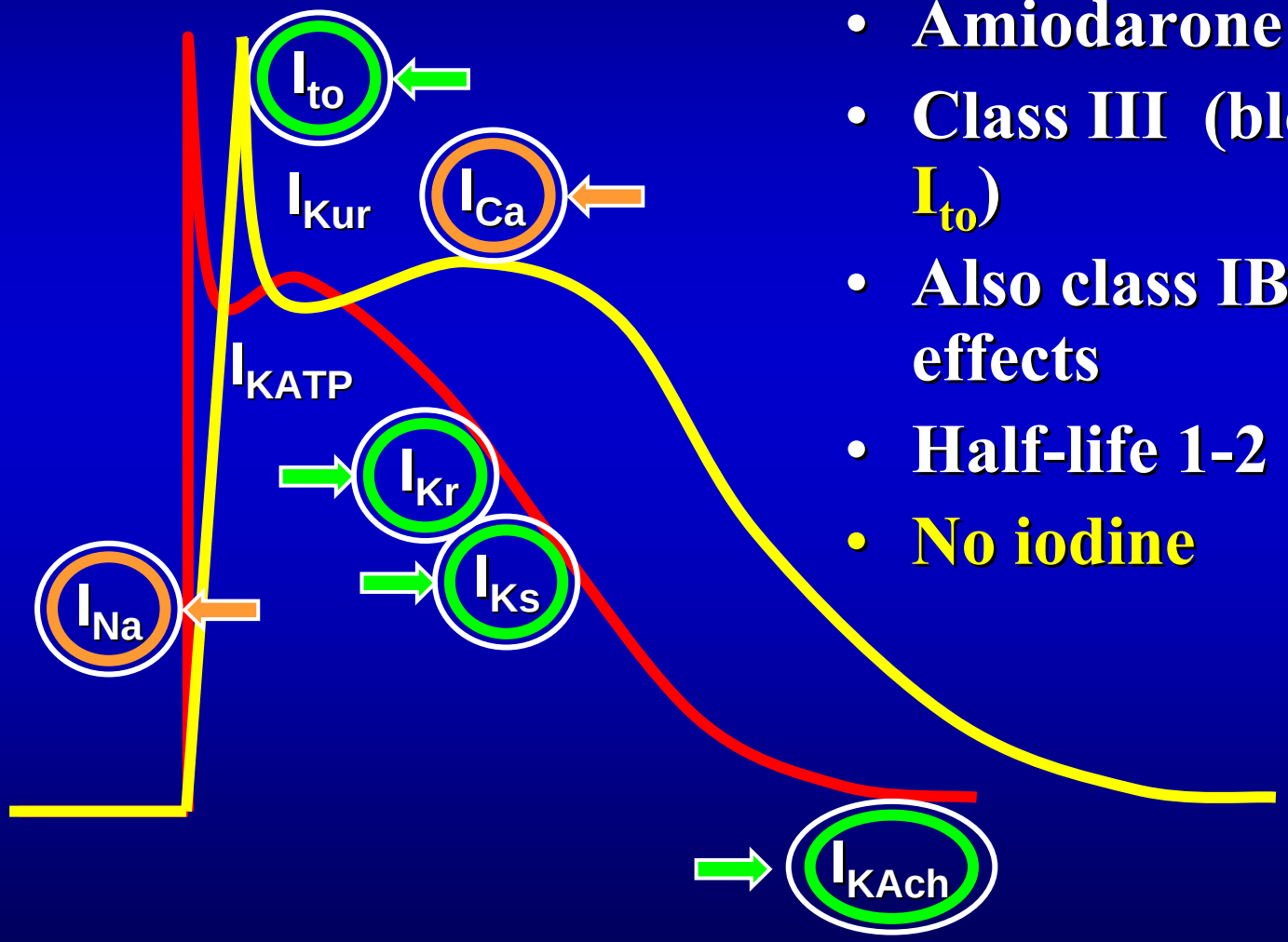




Dronedarone

Wei Sun, *et al. Circulation* 1999;100:2276–2281

Dronedarone

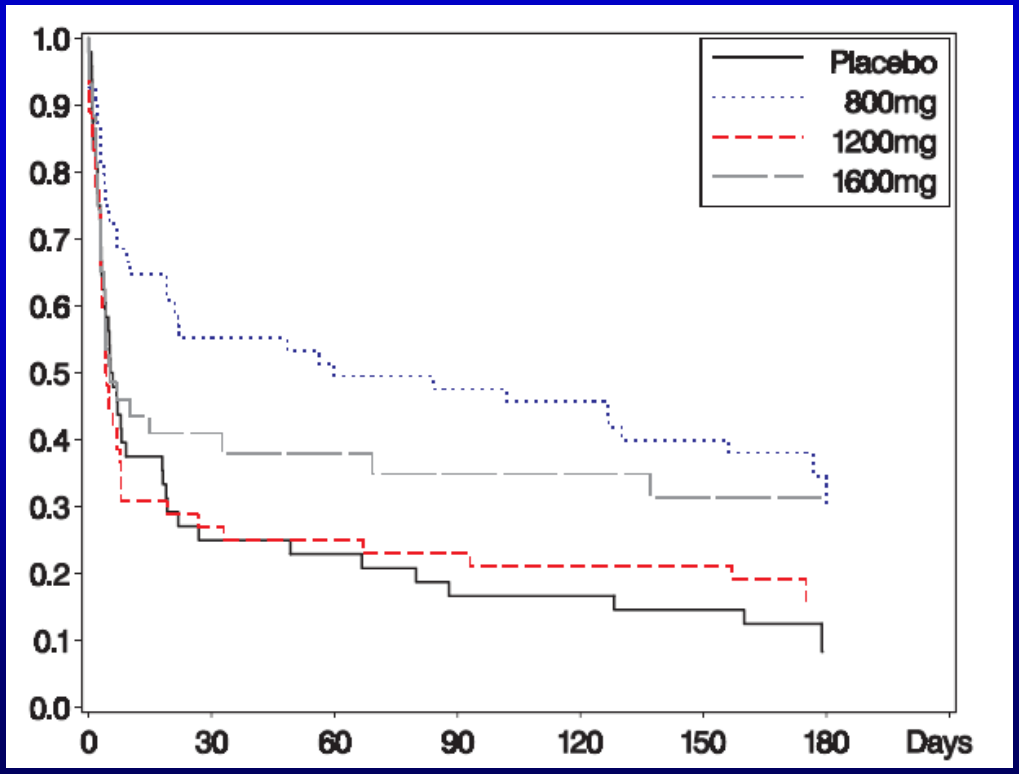


- Amiodarone analogue
- Class III (block I_{Kr}, I_{Ks}, I_{to})
- Also class IB, II, IV effects
- Half-life 1-2 days
- No iodine

DAFNE study

199 Patients with persistent AF and randomized to placebo or 3 dosages of dronedarone

AF recurrences



SR at 6 months:
Dronedarone 35%
Placebo 10 %

No proarrhythmia
QT > 500 sec only with 1600 mg

Toubul EHJ 2003

Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

Bramah N. Singh, M.D., D.Sc., Stuart J. Connolly, M.D., Harry J.G.M. Crijns, M.D., Denis Roy, M.D., Peter R. Kowey, M.D., Alessandro Capucci, M.D., Ph.D., David Radzik, M.D., Etienne M. Aliot, M.D., and Stefan H. Hohnloser, M.D., for the EURIDIS and ADONIS Investigators*

- **1237 pts with at least 1 episode of AF in the previous 3 months randomized in a 2:1 ratio (dronedarone/placebo)**

Mean age: 63 years, mean EF 58%

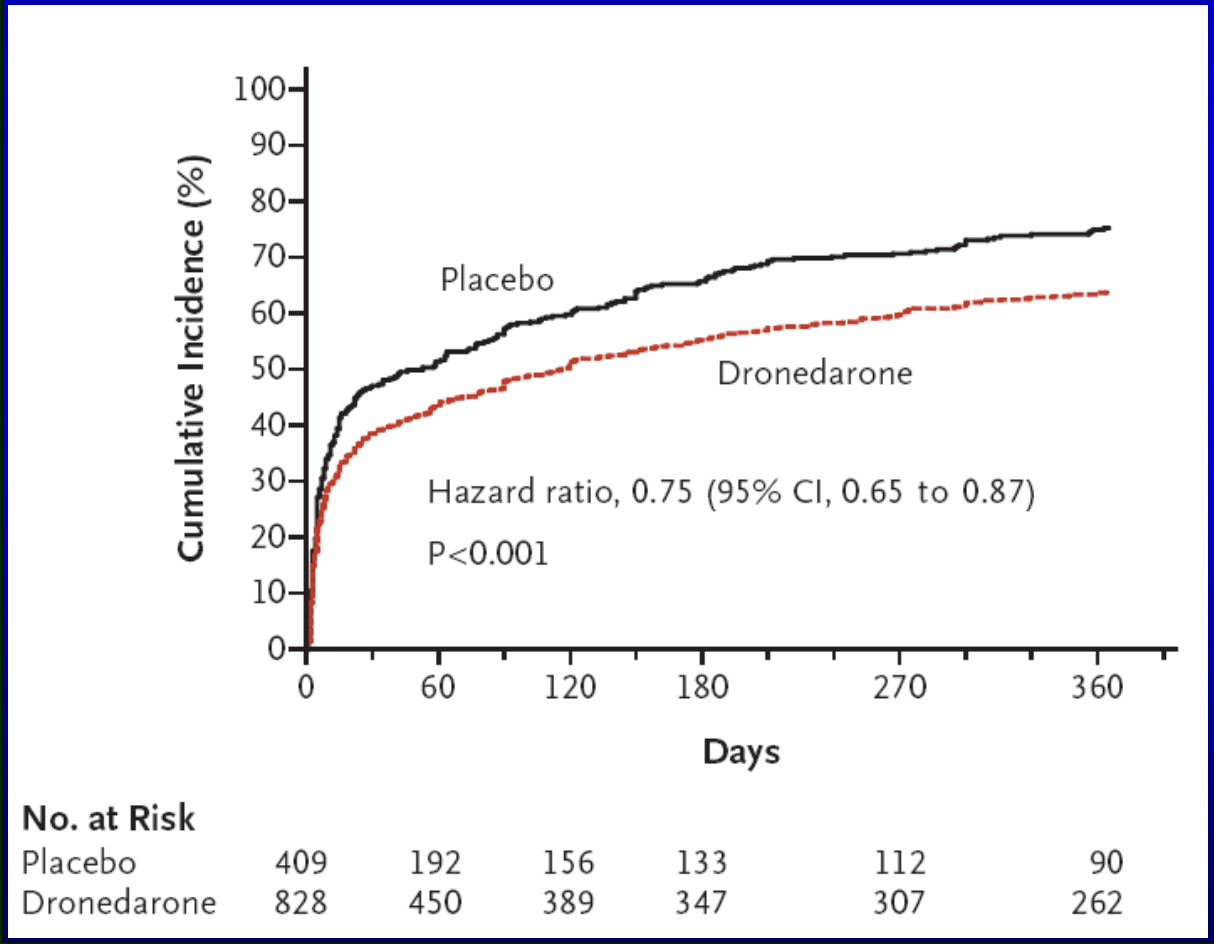
- **Exclusion: pts with NHYA class III-IV, bradycardia< 50/min, creatinine > 1,7 mg**

- **Dronedarone 800 mg. F-up 1 year (visits and TTM)**

Singh, NEJM Settembre 2007

Euridis-Adonis

primary endpoint



Primary endpoint

Prolongation of time to first recurrence

(116 vs 53 days)

Secondary endpoints

Ventricular response reduction

(102 vs 117 bpm)

Hospitalization reduction

(21 vs 32% pts)

Singh, NEJM 2007;357

Euridis-Adonis: side effects

- **No proarrhythmic effect**

  (no episodes of TdP, ventricular arrhythmia: 0,7 vs 0,5%)

- **Pulmonary, hepatic and thyroid effects similar to placebo**

Singh, NEJM 2007;357

ANDROMEDA:

ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse

Mortality trial with dronedarone compared to placebo in patients with moderate to severe HF regardless the arrhythmia history

Kober et al: Increased mortality after dronedarone therapy for severe heart failure NEJM 2008;358: 2678-2687

ANDROMEDA

- 627 consecutive patients
- CHF (NYHA class II–IV) :
  - At least one episode of CHF in the preceding month
  - diuretics
- LVEF <0.35
- Randomized between Placebo and Dronedarone 400mg BID

Kober et al: Increased mortality after dronedarone therapy for severe heart failure NEJM 2008;358: 2678-2687

ANDROMEDA

Population characteristics

	Placebo (n=317)	Dronedarone 400 mg BID (n=310)
Age (years) Mean (SD)	68.8 (12.1)	69.5 (11.5)
Min–Max	27–96	33–90
Weight (Kg) Mean (SD)	79.13 (18.70)	77.72 (17.00)
Gender [n (%)] Male	242 (76.3%)	230 (74.2%)
Race [n (%)] Caucasian	316 (99.7%)	308 (99.4%)
Echocardiography – Wall motion index (WMI)		
Mean (SD)	0.86 (0.23)	0.90 (0.23)
Min–Max	0.3–1.2	0.3–1.2
NYHA class [n (%)]		
CLASS II	118 (37.2%)	126 (40.6%)
CLASS III	186 (58.7%)	178 (57.4%)
CLASS IV	13 (4.1%)	6 (1.9%)
Creatinine clearance [n (%)]		
<50 ml/min	128 (41.7%)	133 (44.2%)
≥ 50 ml/min	179 (58.3%)	168 (55.8%)

ANDROMEDA study

Early discontinuation of the study at 2 month f/up : significant increase in mortality in the dronedarone group compared to placebo (8,1%vs 3.8%)

Retrospectively: higher mortality in patients in which ACEi or ARB were discontinued for creatinine increase.

Kober et al: Increased mortality after dronedarone therapy for severe heart failure NEJM 2008;358: 2678-2687

ATHENA TRIALS STUDY DESIGN

Qualifying patients with paroxysmal / persistent AF

4628 pts

hemodynamically stable

minimum 12 month follow-up

- **age ≥ 75 years or ≥ 70 years with ≥ 1 risk factor:**

hypertension; diabetes; prior stroke/TIA; LA ≥ 50 mm; LVEF≤ 0.40

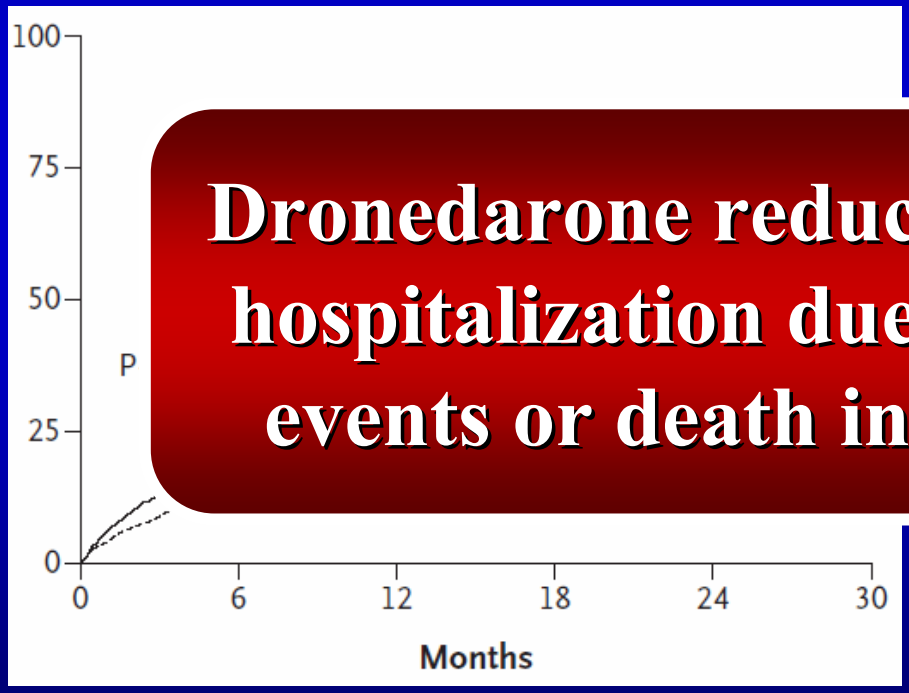
Dronedarove 400 mg BID vs Placebo

	Placebo (N=2327)	**Dronedarone** (N=2301)	All patients (N=4628)
History of CHF NYHA II/III	**515 (22%)**	**464 (20%)**	**979 (21%)**
LVEF< 0.45	**285/2281 (13%)**	**255/2263 (11%)**	**540/4544 (12%)**
LVEF< 0.35	**87/2281 (4%)**	**92/2263 (4%)**	**179/4544 (4%)**

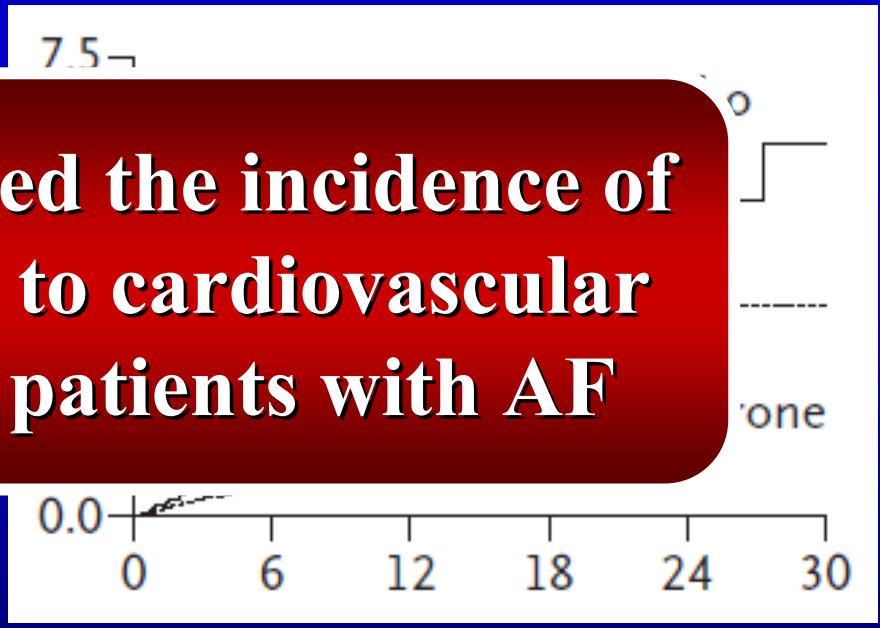
N Engl J Med 2009;360:668-78

Primary Endpoint

TIME TO FIRST CARDIOVASCULAR HOSPITALIZATION OR DEATH



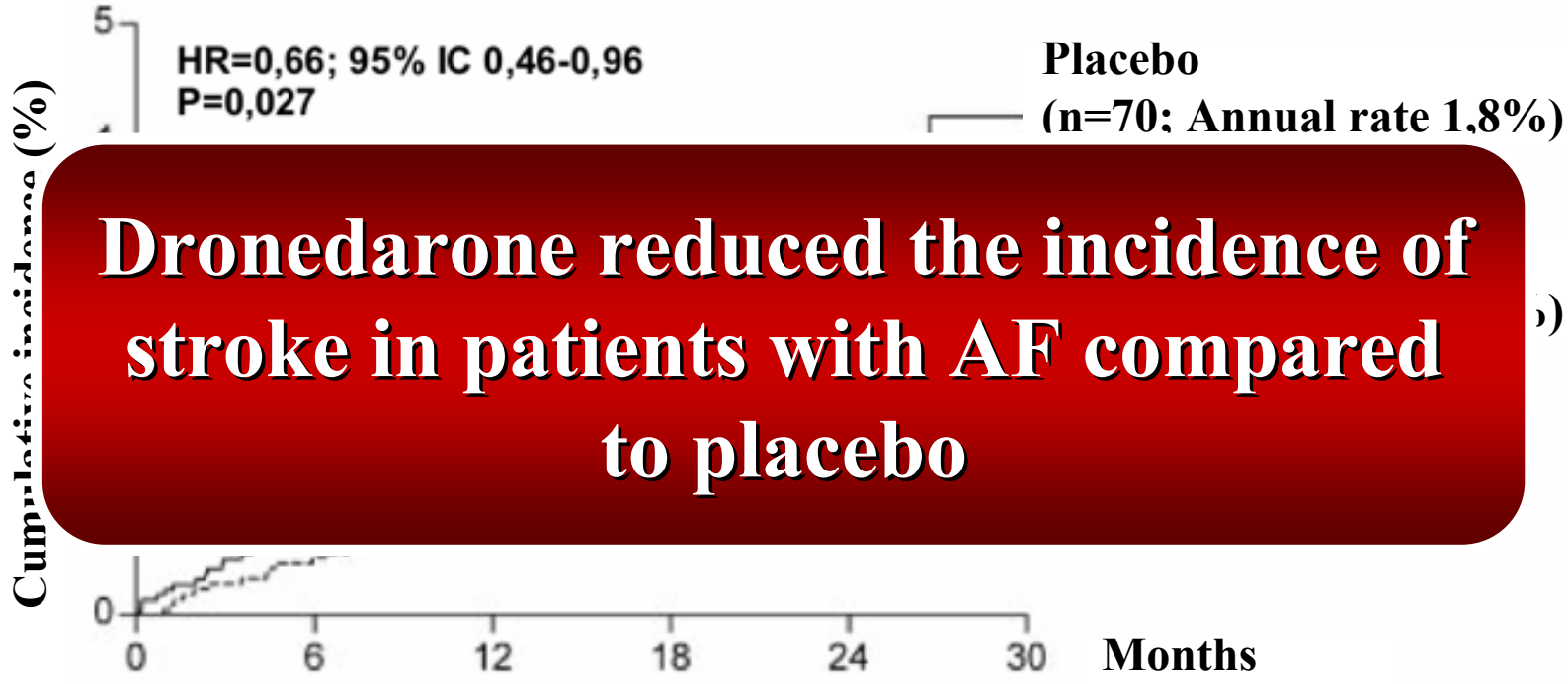
CARDIOVASCULAR MORTALITY



Dronedarone reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF

N Engl J Med 2009;360:668-78

Post-hoc analysis of stroke in ATHENA trial



Dronedarone reduced the incidence of stroke in patients with AF compared to placebo

Connolly et al.: Circulation 2009 120 (13): 1174-80

Studio DIONYSOS (risultati preliminari)

504 pazienti con **FA persistente cardiovertiti** e randomizzati a dronedarone (400mg) e amiodarone (600mg per 28 gg e poi 200mg al dì)

End-point primario: Fibrillazione atriale documentata all'ecg o interruzione del farmaco per intolleranza o inefficacia

Follow-up medio di 7 mesi: 55, 3% dei pazienti trattati con amiodarone hanno raggiunto l'endpoint primario contro il 73,4% dei pazienti trattati con dronedarone

Minori effetti cardiaci avversi (bradicardia e prolungamento del QT) e un maggior numero di effetti collaterali gastrointestinali si sono verificati nel braccio trattato con dronedarone

AF and Dronedarone

Summary

- Demonstrated efficacy vs placebo. Preliminary results do not prove a better efficacy compared to amiodarone but it presents a better risk profile
- No negative inotropic effect (in moderate heart failure with creatinine <1.6mg/dl)
- No systemic side effects (no thyroid and pulmonary side effects)
- No Torsade de Pointes reported

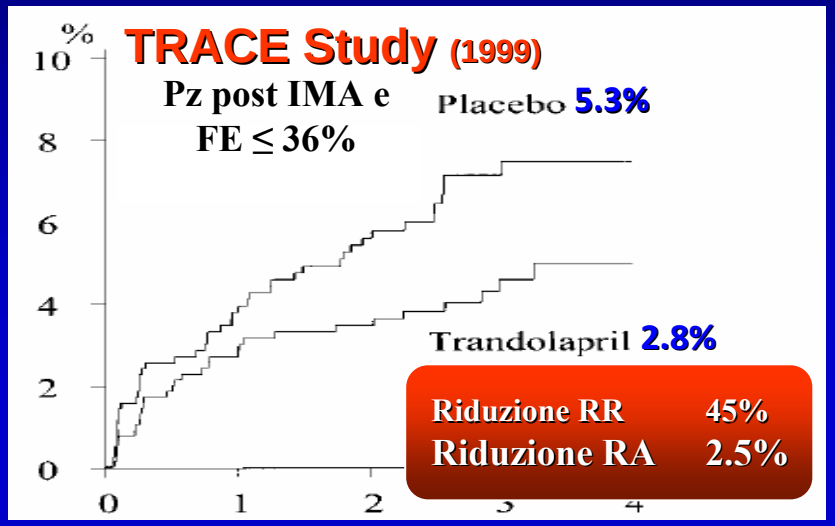
Therapeutic strategies

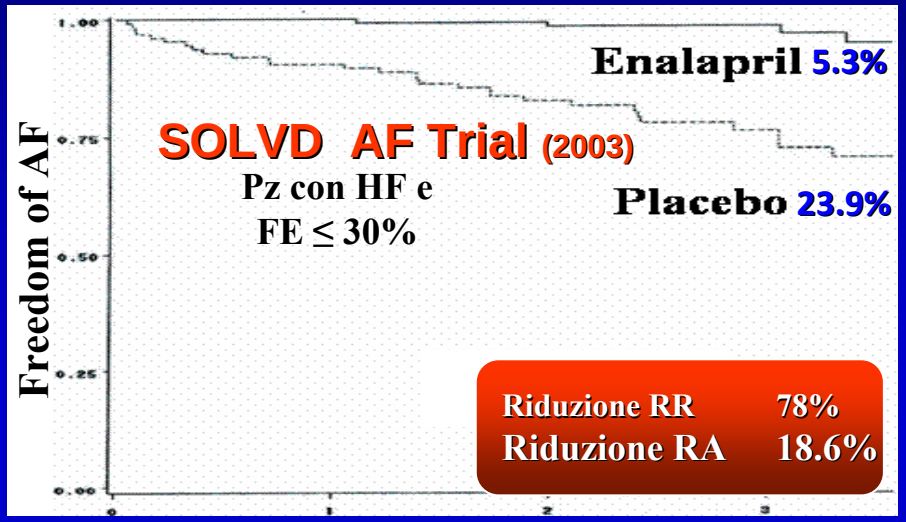
Antiarrhythmic drugs

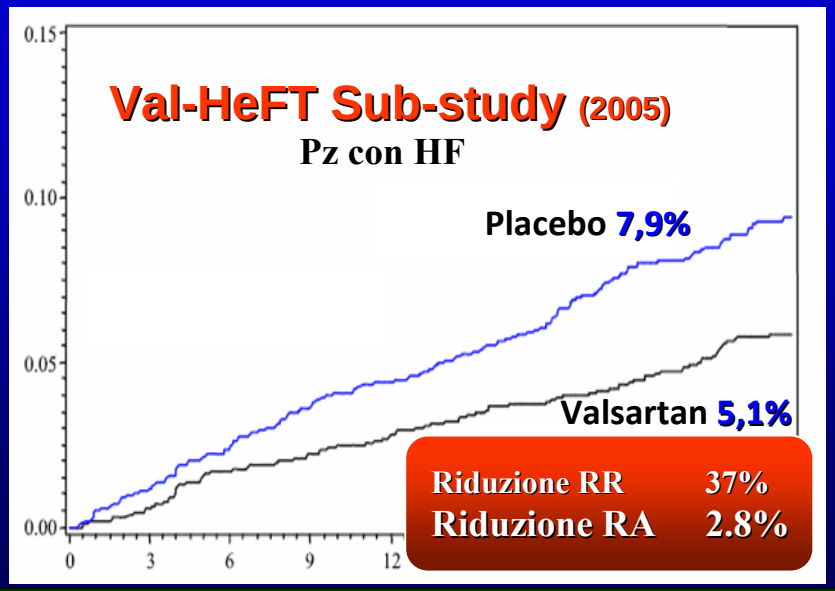
Substrate altering drugs

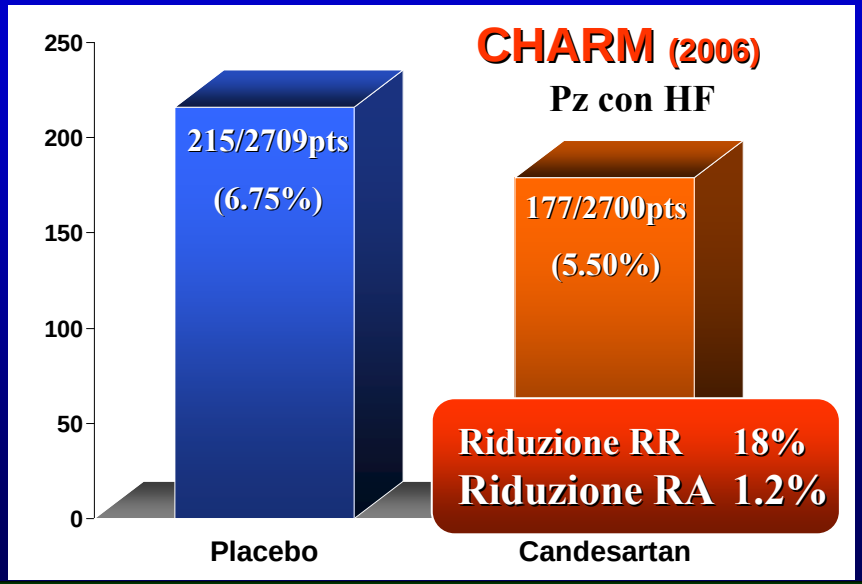
Ablative therapy

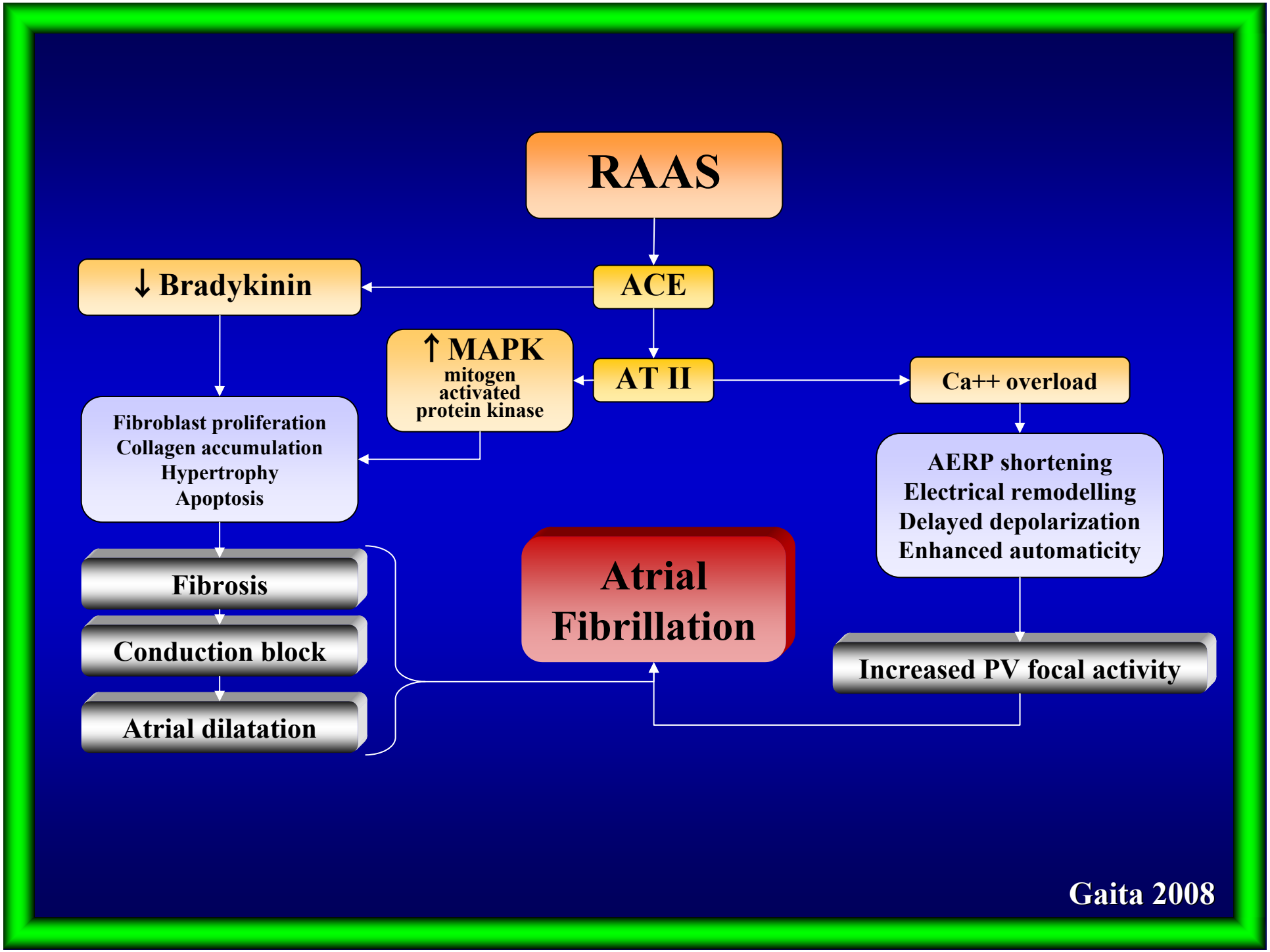
AF incidence in pts with heart failure treated with ACE-i or Angiotensin II receptor blockers










RAAS
ACE
↓ Bradykinin
↑ MAPK
mitogen
activated
protein kinase
AT II
Ca++ overload
Fibroblast proliferation
Collagen accumulation
Hypertrophy
Apoptosis
AERP shortening
Electrical remodelling
Delayed depolarization
Enhanced automaticity
Fibrosis
Conduction block
Atrial dilatation
Atrial
Fibrillation
Increased PV focal activity
Gaita 2008

Irbesartan in AF prevention

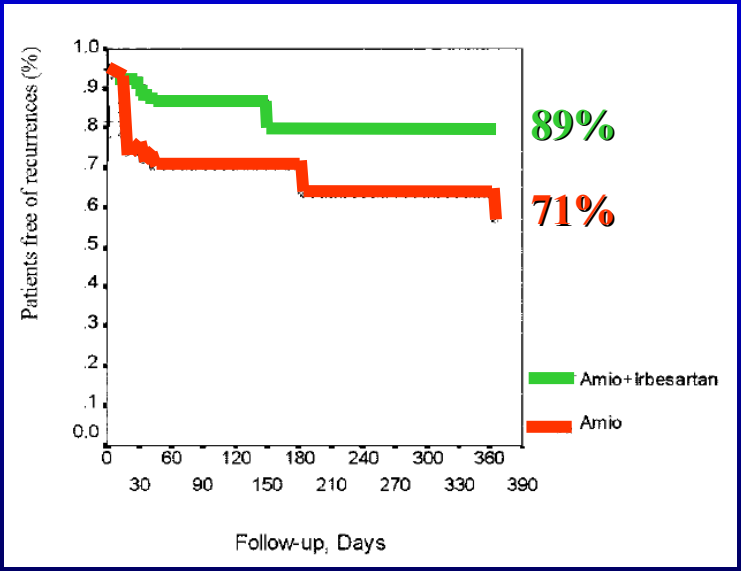
Use of Irbesartan to Maintain Sinus Rhythm in Patients With Long-Lasting Persistent Atrial Fibrillation

A Prospective and Randomized Study

22pts Amiodarone
29.0%

AF cases after mean follow-up of 254 days

9pts Amiodarone + Irbesartan
11.0%



Reduction RR 35%
Reduction RA 18%

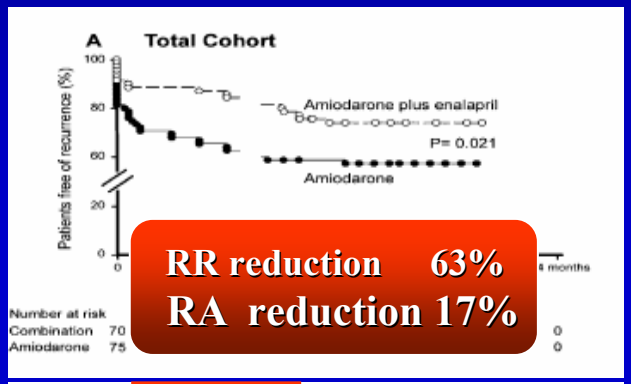
Madrid A, Circulation 2002;106:331-336

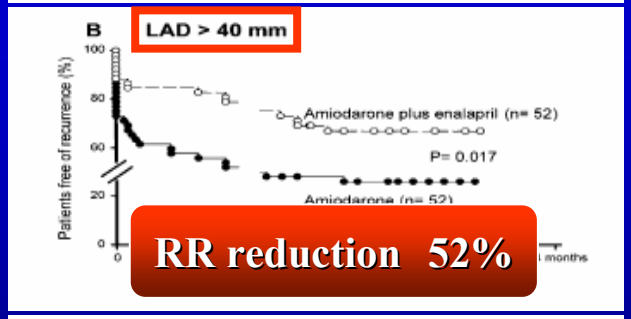
Enalapril in the SR maintenance in pts with persistent AF underogoing ECV

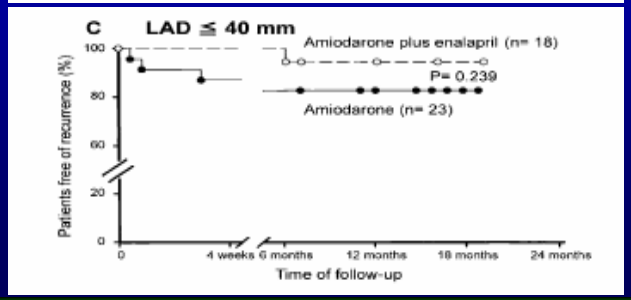
145pts with AF
(30% hypertensive, 16% valvular)

- **70**pts Amiodarone + Enalapril
- **75**pts Amiodarone

} ECV







SR after follow-up 270 giorni

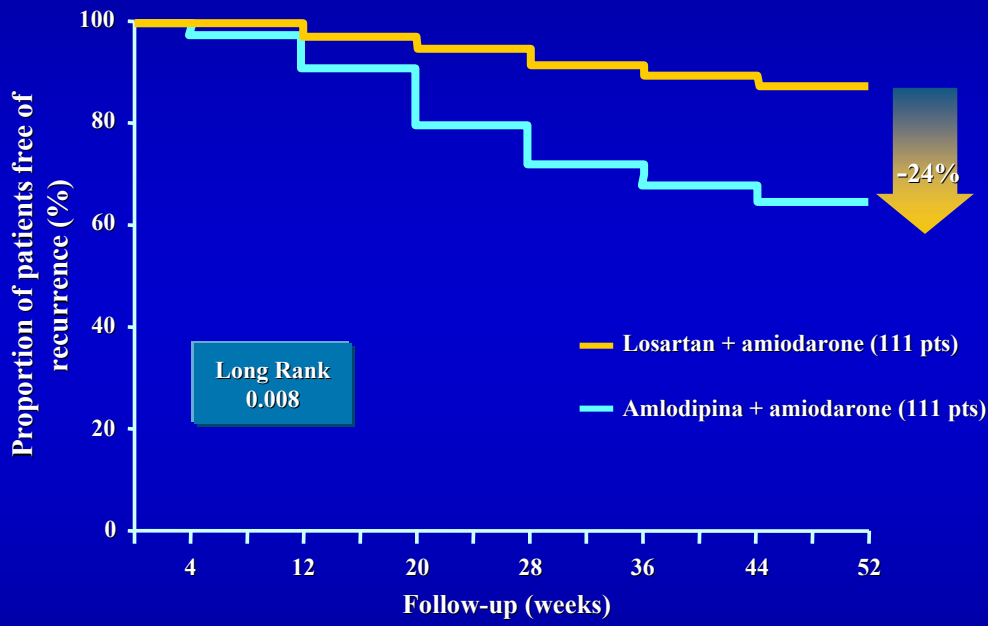
ACEi	74.3% (52/70pts)
no ACEi	57.3% (43/75pts)

104/145pz LA > 40mm

Enalapril reduces AF risk of AF especially in patients with LA > 40mm

Ueng KC et al. Eur Heart J 2003; 24:2098

Losartan: prevention of AF recurrences in hypertensive patients



222pz
PAF and hypertension

111pz
Amiodarone + Amlodipina

111pz
Amiodarone + Losartan

AF recurrences after a mean f-up of 299 giorni

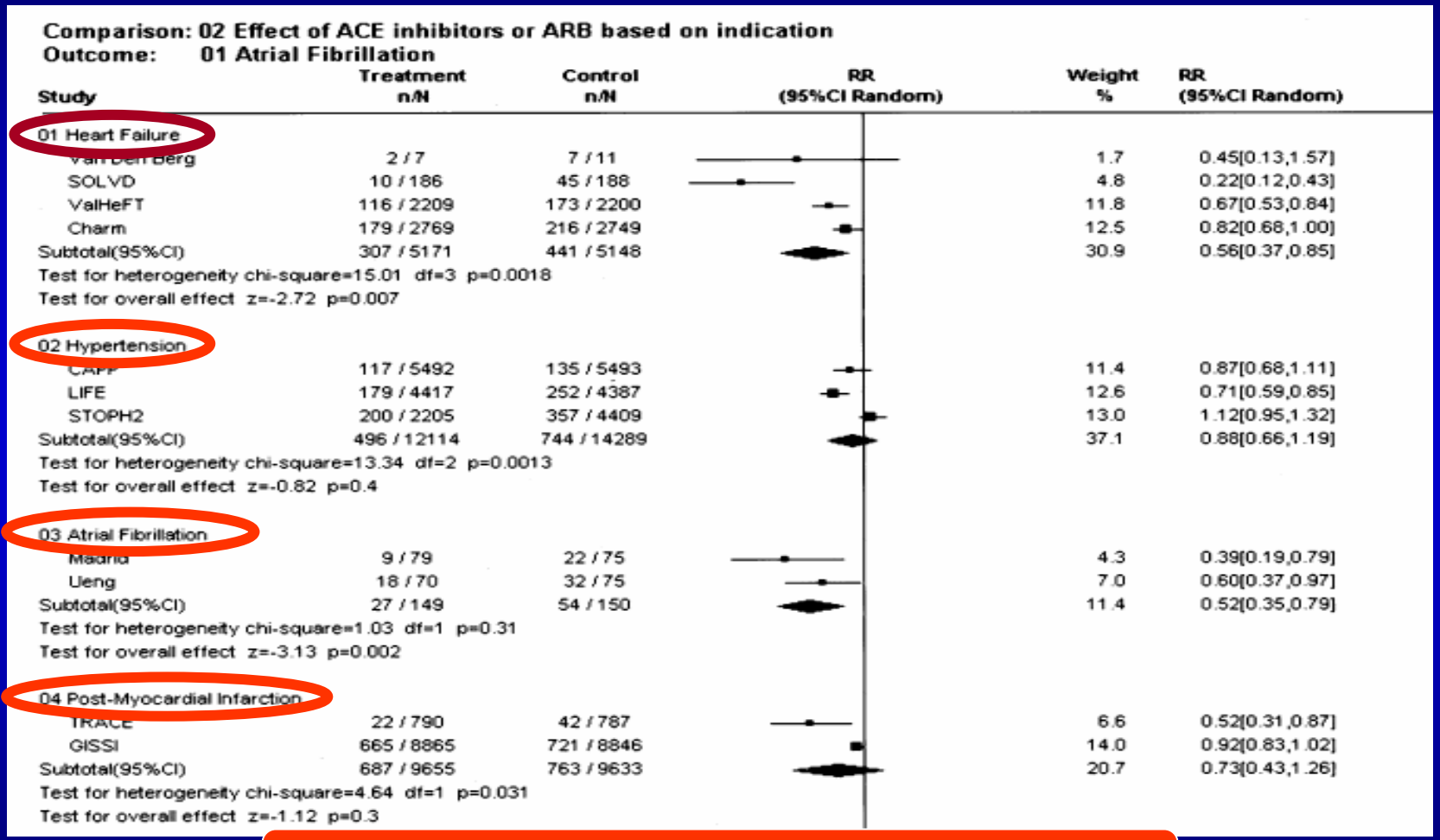
39/111 pts (35%)
Amiodarone + Amlodipina

13/111 pts (11%)
Amiodarone + Losartan

RA reduction 24%

Fogari R et al. J Cardiovasc Pharmacol 2006;47:46-50

Metanalysis(2005): different studies for different pathologies



Relative risk reduction of 28%

…which increases to 44% in pts with HF

Healey et al. JACC 2005

Valsartan for prevention of recurrent atrial fibrillation
GISSI-AF Investigators

57% of pts with ACE-I

1442 pts

62% M, age 67 yrs, 85% hypertensive, 8% HF

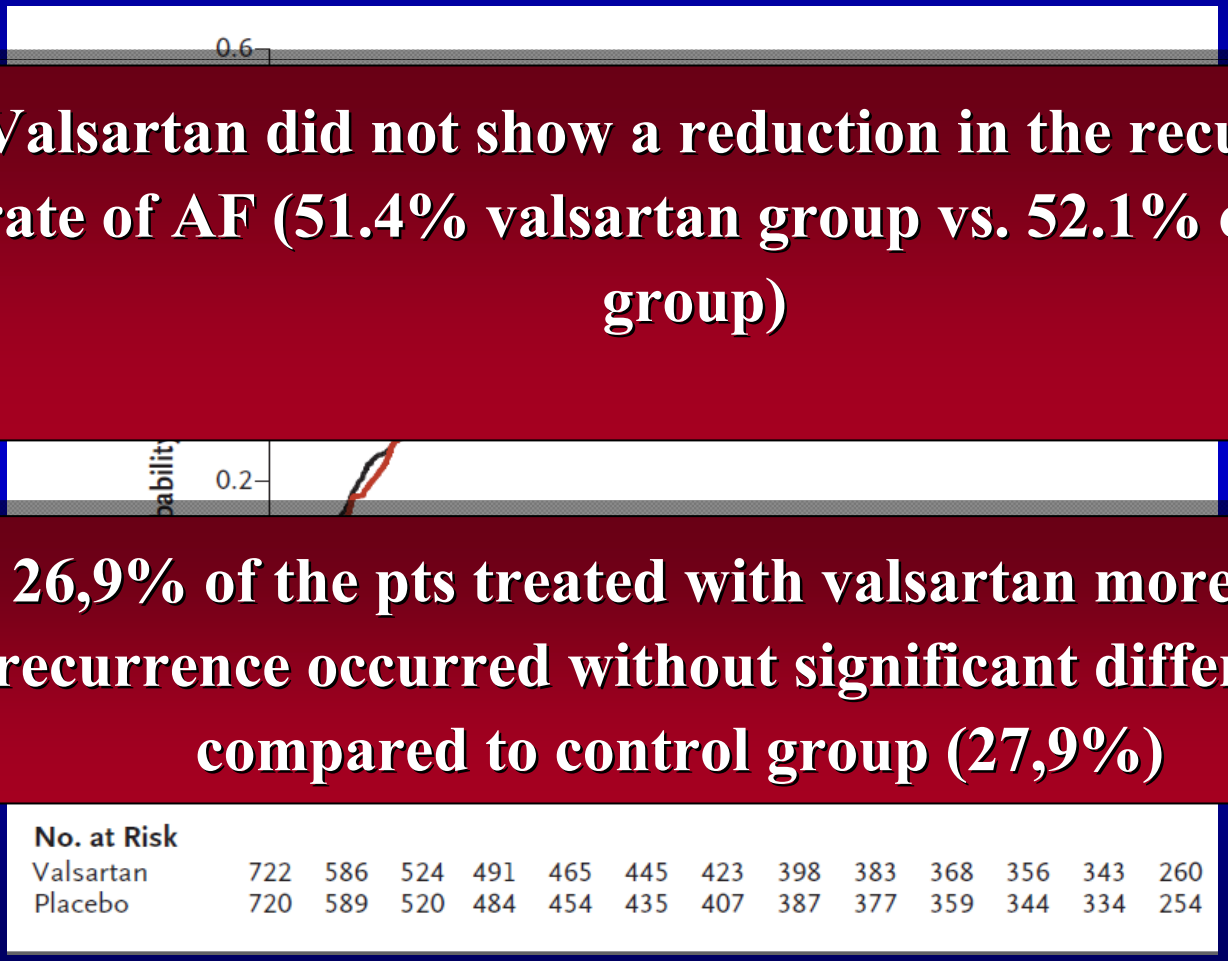
Hx of AF in the last 6 months, but in SR at the time of enrollment

722 pts
Valsartan (80 mg→320 mg)

720 pts
Placebo

N Engl J Med 2009; 360:1606-17

AF recurrences after a follow-up of 1 year



Valsartan did not show a reduction in the recurrence rate of AF (51.4% valsartan group vs. 52.1% control group)

In 26,9% of the pts treated with valsartan more than 1 recurrence occurred without significant difference compared to control group (27,9%)

N Engl J Med 2009; 360:1606-17

ACTIVE-I: Inclusion criteria

- Paroxysmal, persistent or permanent AF
- Evidence of elevated vascular risk (any of the following):
  - Age ≥ 75 yrs
  - On treatment for hypertension
  - Previous stroke, TIA or not CNS embolic event
  - LV systolic dysfunction EF <45%
  - Peripheral vascular disease
  - Age 55 - 74 aa with
    - » Diabetes mellitus on therapy, or
    - » Previous documented MI or documented coronary artery disease

The ACTIVE Investigators *AHJ* 2006;151(6):1187-93

ACTIVE I: Baseline characteristics of the population

	%
Sinus rhythm	irbesartan 18,7 vs placebo 19,6
Heart failure	irbesartan 32,3 vs placebo 31,6
Systolic/ diastolic pressure	irbesartan 138/83 mmHg vs placebo 138/82 mmHg

ESC Congress, Barcelona, Hotline III, 1 September 09

ACTIVE I:
Baseline characteristics of the population

	%
Paroxysmal AF	**irbesartan 19,6 vs placebo 20,5**
Persistent AF	**irbesartan 14,3 vs placebo 14,9**
Permanent AF	**irbesartan 66,0 vs placebo 64,4**

- Mean follow-up : 4.1 years

ESC Congress, Barcelona, Hotline III, 1 September 09

ACTIVE-I: Endpoints

- **Primary End-point:**
- ✓ **Stroke, myocardial infarction vascular death**
- ✓ **Stroke, myocardial infarction vascular death CHF hospitalization**

- **Secondary end-points**
  - **Total mortality**
  - **Stroke**
  - **CHF hospitalizations**
  - **CHF hospitalizations or hospitalizations for any cause**

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ACTIVE-I: Preliminary results

PRIMARY First occurrence of one of the following events	INCIDENCE	HR	p
Stroke, MI or vascular death	placebo 5,4% vs irbesartan 5,4%	0,99	NS
Stroke, MI or vascular death or hospitalization for CHF	placebo 7,7% vs irbesartan 7,3%	0,94	NS

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ACTIVE-I: Preliminary results

SECONDARY END-POINTS	REDUCTION	HR	p
stroke	-9%	0,91	0,2 NS
Hospitalizations for CHF	-14%	0,86	0,019
Any case of CHF	-12%	0,88	0,014
Hospitalizations for CHF o any episode of CHF	NA	NA	NS
Total mortality	NA	NA	NS

ESC Congress, Barcelona, Hotline III, 1 September 09

Therapeutic strategies

Antiarrhythmic drugs

Substrate altering drugs

Ablative therapy

Therapy for AF: present and future

- Different treatments are available
- From “rate or rhythm control” to multimodality treatment model
- Aim: improving quality of life, reducing stroke risk and improving mortality