

Νεώτερα φάρμακα για τη θεραπεία της κολπικής μαρμαρυγής

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Σεμινάριο Ομάδων Εργασίας

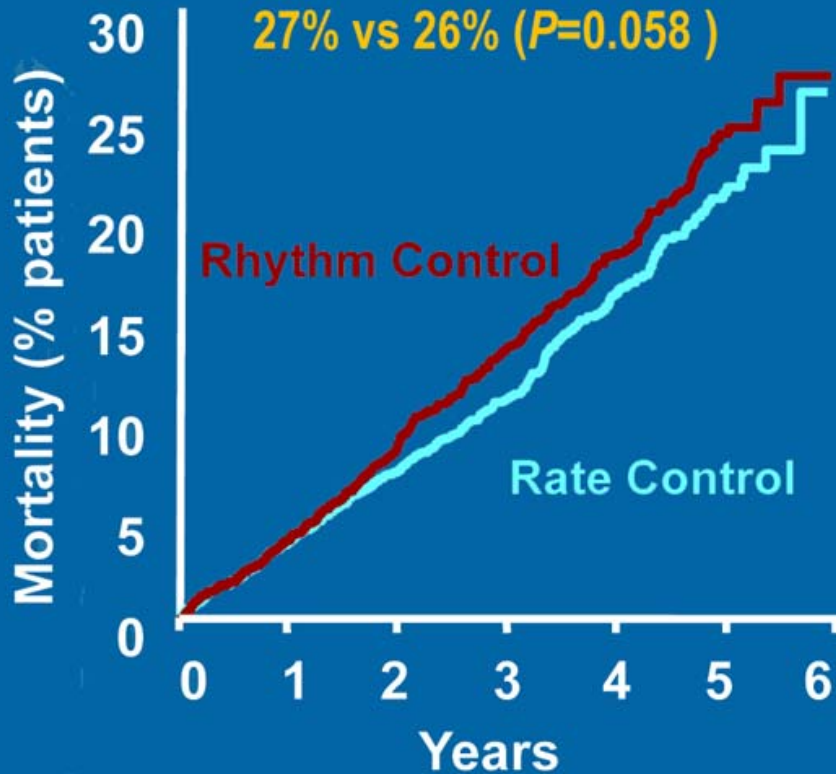
Θεσσαλονίκη, 18-20 Φεβρουαρίου 2010

AFFIRM : Main Results

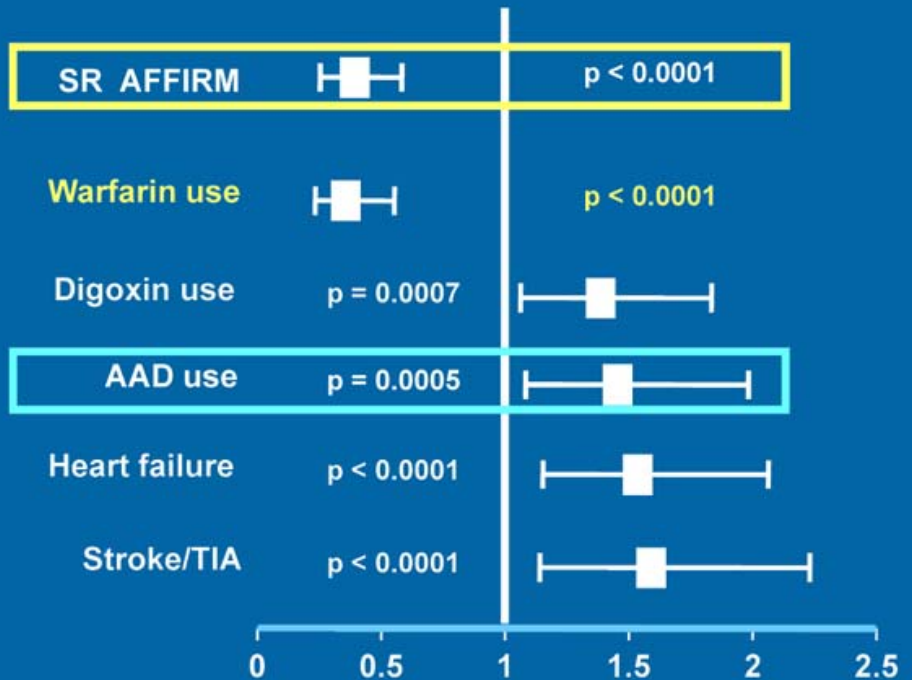
AFFIRM

All-cause Death

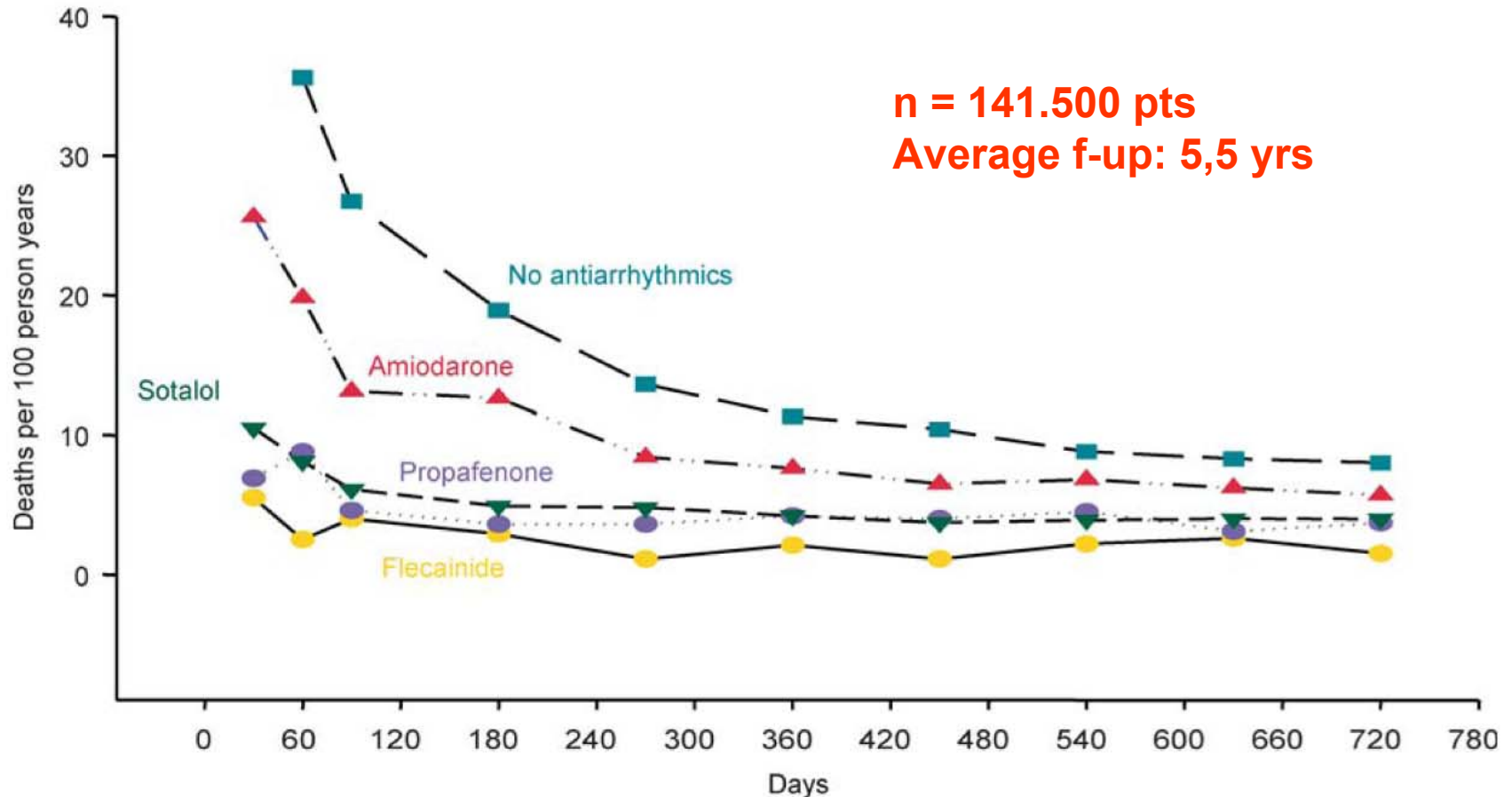
27% vs 26% ($P=0.058$)



Hazard Ratio



Antiarrhythmic Therapy and risk of death in patients with AF

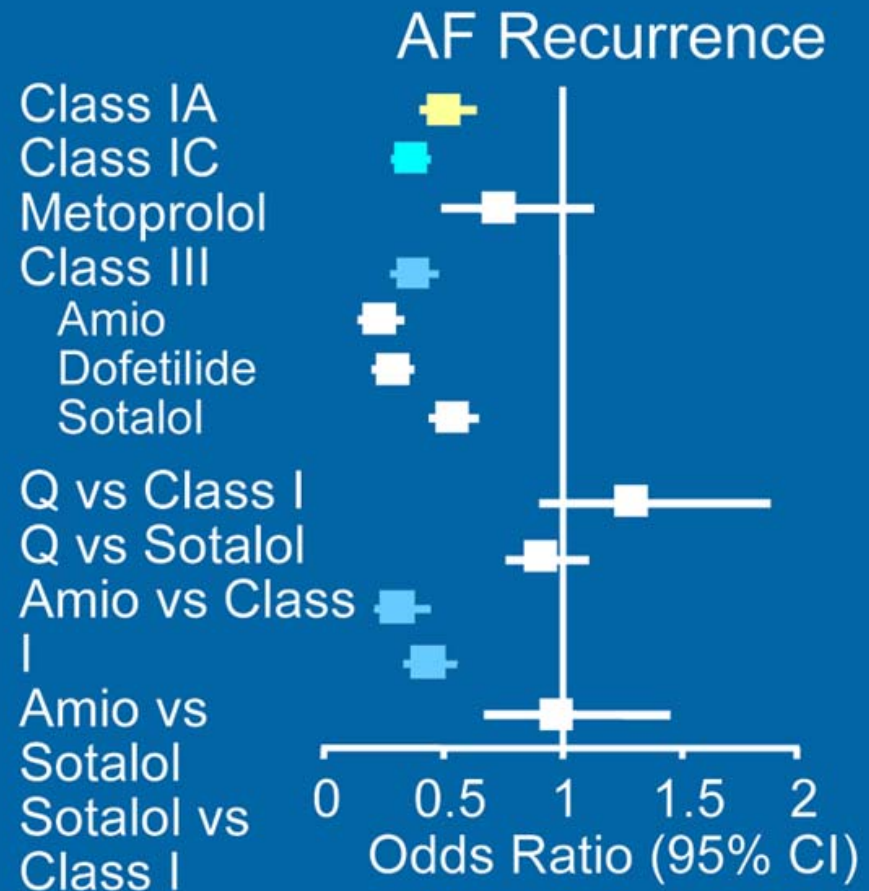


Incidence rates for deaths in all treatment groups and in the population receiving no antiarrhythmics.

AADs for Prevention of AF after DCC

Systematic Review of RCTs

RCT included into analysis	
Total	44
No. of patients	11,322
Placebo controlled	25
Active comparator	14
Persistent AF	38 (60% pts)
PAF/recent onset	6
EF > 50%	41
Lone AF	1
Follow-up	1 year



Class Ia: Disopyramide, Quinidine and Procainamide

Beta Blocker
Antiarrhythmic Agents
New and Old

Class III

Class Ic

Amiodarone

Sotalol

Propafenone

Flecainide

**Budio-
darone
Next-
erone**

**New
Class III Agents**

**Upstream
therapies**

Novel Drugs

Dofetilide

Azimilide

**SAC
Blockers**

Rotagaptide

Celivarone

Dronedarone

Ranolazine

**Na⁺/H⁺
Inhibitor**

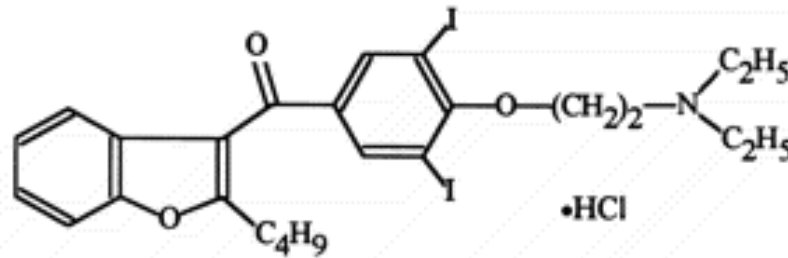
Multi-channel blockers

**Na⁺/Ca²⁺
Inhibitor**

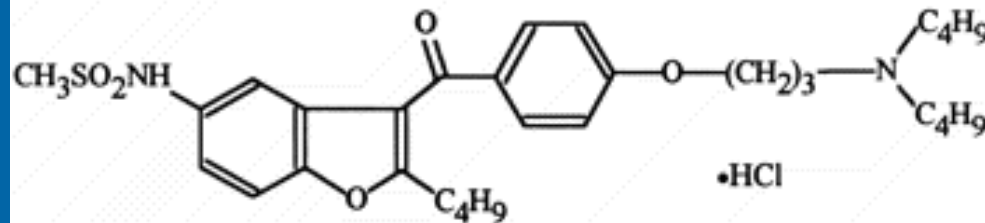
**Adenosine
Agonist**

**Vernakalant
Xen D0101**

Dronedarone structural formula 2/2



Amiodarone (MW=682)



SR33589B/Dronedarone (MW=593)

(Wei Sun, JSM Sarma, BN Singh, *Circulation*, 1999 ; 100 : 2276-2281)

Dronedarone development program

Rhythm and Rate Control	N	Population	Objectives
DAFNE	270	AF	Efficacy and safety in AF cardioversion and maintenance of sinus rhythm
EURIDIS	612	AF/AFL	Maintenance of sinus rhythm in AF/AFL
ADONIS	625	AF/AFL	Maintenance of sinus rhythm in AF/AFL
ERATO	174	Permanent AF	Ventricular rate control
DIONYSOS	504	AF	Reduction of recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy
Special Populations			
ANDROMEDA	627	Recent severe episode CHF and LV dysfunction	Reduction of hospitalization for worsening heart failure or death in patients with unstable severe CHF with LVD
Clinical Outcomes			
ATHENA	4628	AF/AFL	Reduction of cardiovascular hospitalization or death from any cause in patients with AF/AFL

Inclusion and Exclusion Criteria

Inclusion criteria

- High-risk patients with a history of paroxysmal or persistent AF/AFL
- Aged ≥ 75 years with or without additional risk factors
- Aged ≥ 70 years and ≥ 1 risk factor (hypertension; diabetes; prior stroke/TIA; LA ≥ 50 mm; LVEF < 0.40)

- ▶ **Originally the protocol had allowed patients < 70 years of age with additional risk factors into the study**
- ▶ **The protocol was subsequently amended to include only patients ≥ 70 years of age**

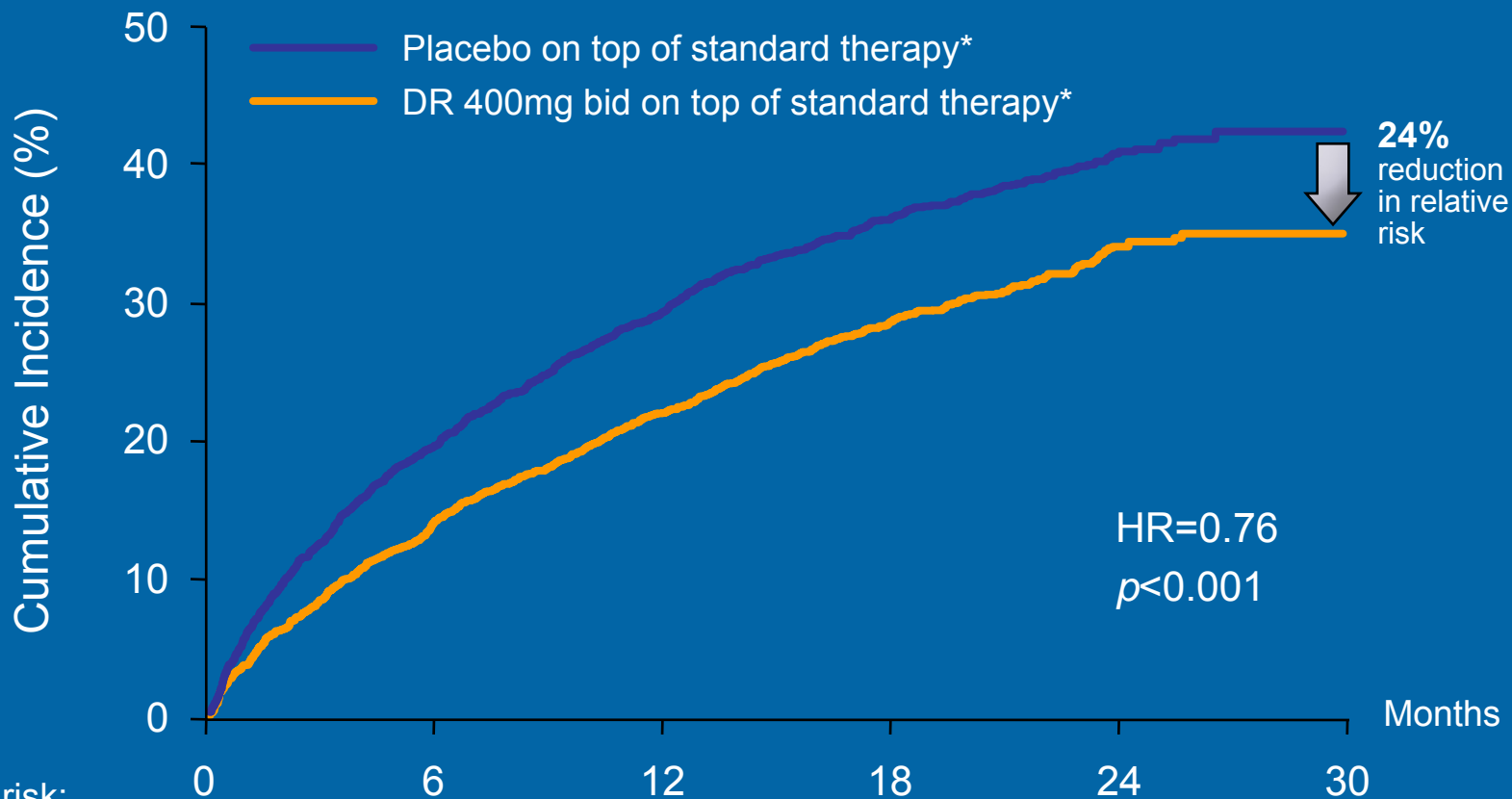
Exclusion criteria

- Permanent AF
- Unstable hemodynamic situation (i.e. recently decompensated CHF)
- CHF NYHA class IV
- Bradycardia < 50 bpm and/or PR > 0.28 sec
- Sick sinus syndrome
- Calculated GFR at baseline < 10 ml/min
- Potassium < 3.5 mmol/L
- Concomitant antiarrhythmic drug Rx
- Severe illness limiting life expectancy
- Pregnancy or breastfeeding
- Refusal or inability to give informed consent

Baseline Patient Characteristics

	Placebo n=2327	Dronedarone n=2301	All patients n=4628
Age (mean \pmSD, years)	71.7 \pm 9.0	71.6 \pm 8.9	72 \pm 9.0
<65yr	442 (19.0%)	431 (18.7%)	873 (18.9%)
65 to 75yr	907 (39.0%)	923 (40.1%)	1830 (39.5%)
\geq75yr	978 (42.0%)	947 (41.2%)	1925 (41.6%)
Female gender	1038 (44.6%)	1131 (49.2%)	2169 (46.9%)
AF/AFL at baseline	586 (25.2%)	569 (24.7%)	1155 (25.0%)
Structural heart disease	1402 (60.9%)	1330 (58.3%)	2732 (59.6%)
Hypertension	1996 (85.8%)	1999 (86.9%)	3995 (86.3%)
Coronary heart disease	737 (31.7%)	668 (29.0%)	1405 (30.4%)
Valvular heart disease	380 (16.3%)	379 (16.5%)	759 (16.4%)
Non-ischemic cardiomyopathy	131 (5.6%)	123 (5.3%)	254 (5.5%)
History of CHF NYHA II/III	515 (22.1%)	464 (20.2%)	979 (21.2%)
LVEF <0.45	285/2281 (12.5%)	255/2263 (11.3%)	540/4544 (11.9%)
LVEF <0.35	87/2281 (3.8%)	92/2263 (4.1%)	179/4544 (3.9%)
Lone atrial fibrillation	139 (6.0%)	140 (6.1%)	279 (6.0%)
Pacemaker	243 (10.4%)	214 (9.3%)	457 (9.9%)

Dronedarone Significantly Decreased Risk of CV Hospitalisation or Death by 24%



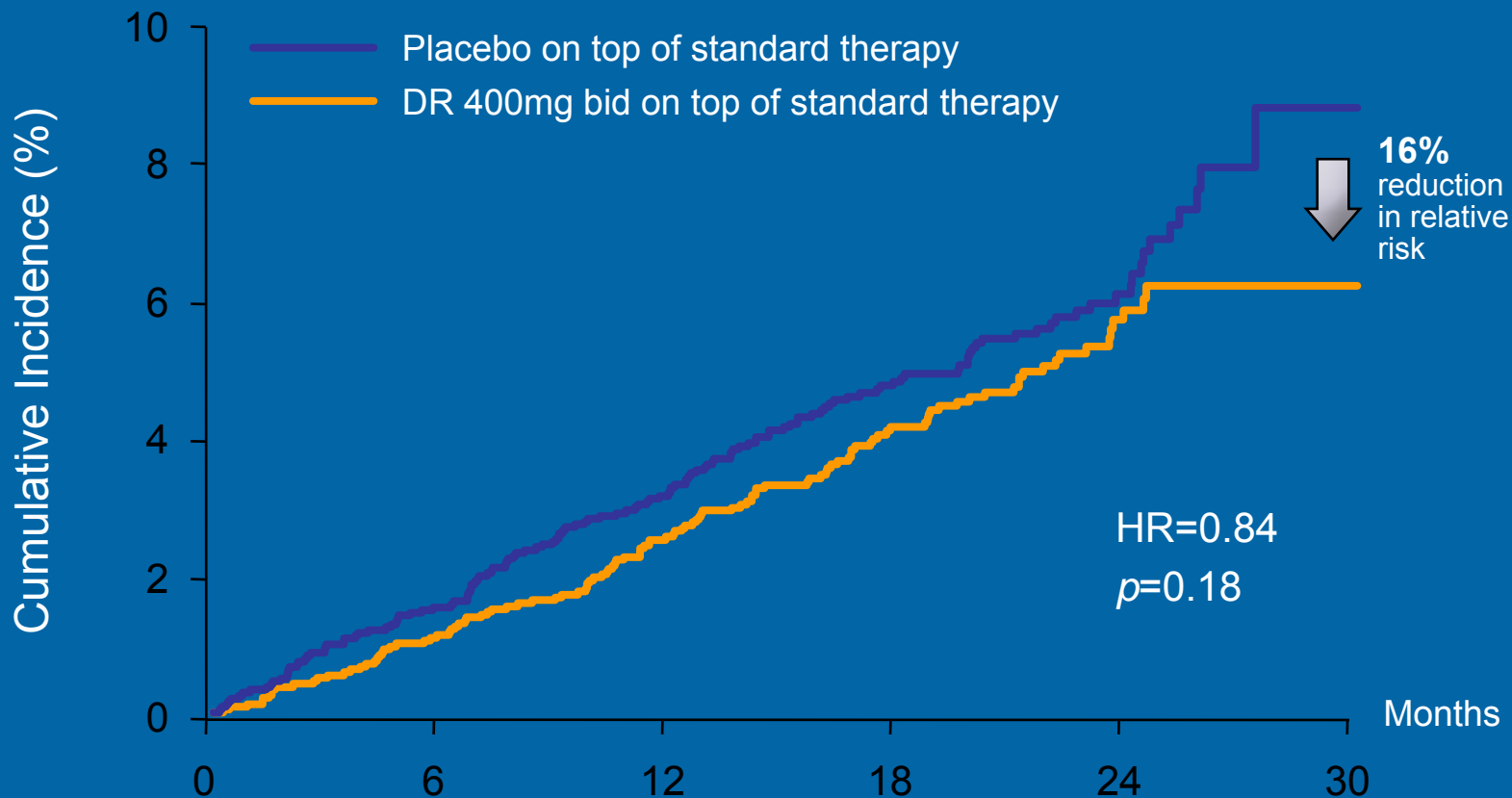
Patients at risk:

	0	6	12	18	24	30
Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

* 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.

Hohnloser SH *et al. N Engl J Med* 2009;360:668-78.

Dronedarone Reduced Risk of All-cause Death by 16%



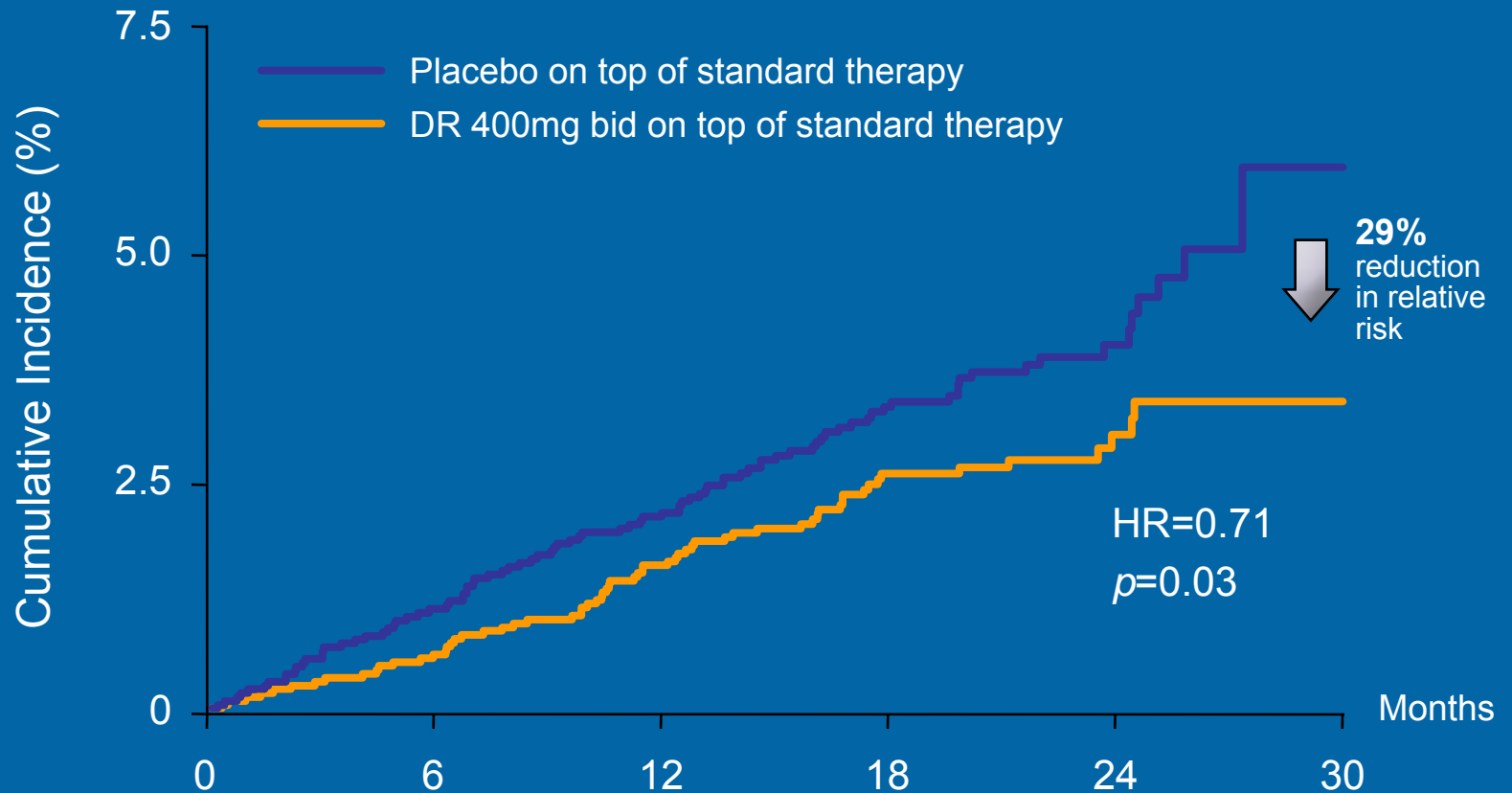
Patients at risk:

Placebo	2327	2290	2250	1629	636	7
DR 400mg bid	2301	2274	2240	1593	615	4

Mean follow-up 21 ±5 months.

Hohnloser SH et al. *N Engl J Med* 2009;360:668-78.

Dronedarone Significantly Decreased Risk of Cardiovascular Death by 29%



Patients at risk:

Placebo	2327	2290	2250	1629	636	7
DR 400mg bid	2301	2274	2240	1593	615	4

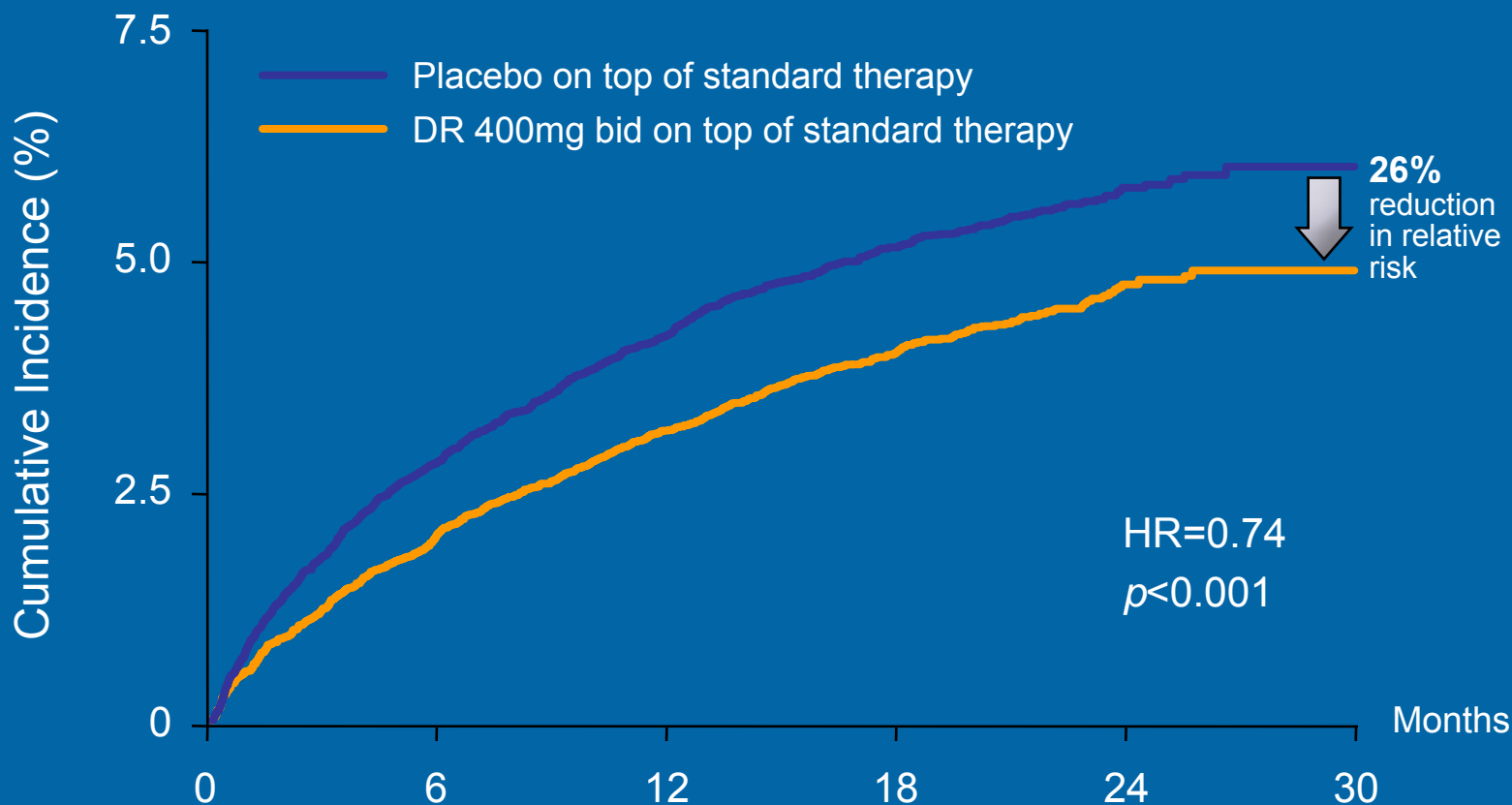
Mean follow-up 21 ±5 months.

Hohnloser SH *et al.* *N Engl J Med* 2009;360:668-78.

Dronedarone Significantly Decreased Risk of Arrhythmic Death by 45% and CV death by 29%

	Placebo n=2327	Dronedaron e n=2301	HR	95% CI	<i>p value</i>
All death	139	116	0.84	0.66; 1.08	0.18
Non-cardiovascular death	49	53	1.10	0.74; 1.62	0.65
Cardiovascular death	90	63	0.71	0.51; 0.98	0.03
Cardiac non-arrhythmic death	18	17	0.95	0.49; 1.85	0.89
Cardiac arrhythmic death	48	26	0.55	0.34; 0.88	0.01
Vascular non-cardiac	24	20	0.84	0.47; 1.52	0.57

Dronedarone Significantly Decreased Cardiovascular Hospitalisation by 26%



Patients at risk:

Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

Mean follow-up 21 ±5 months.

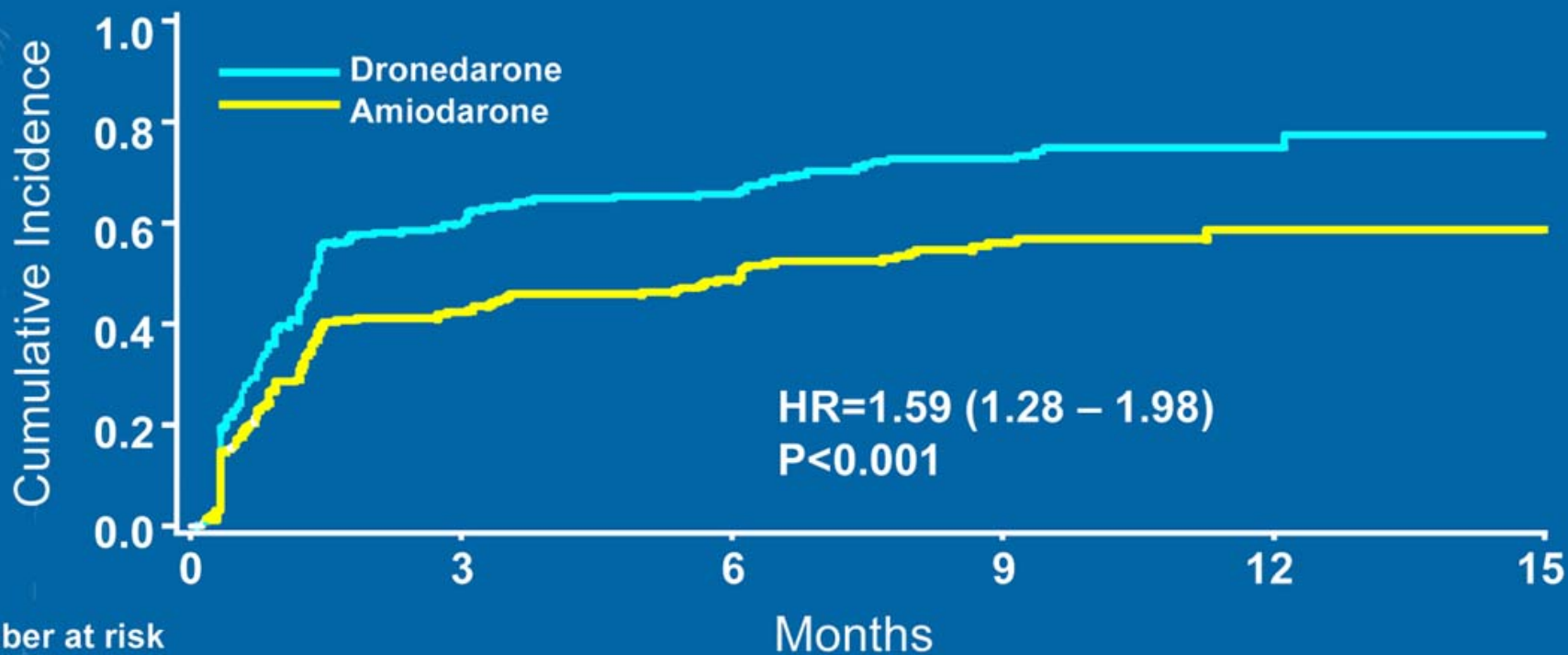
Hohnloser SH *et al.* *N Engl J Med* 2009;360:668-78.

Dronedarone Significantly Decreased Hospitalisations Related to AF by 37%

Reason for first CV hospitalisation	Placebo n=2327	Dronedaron e n=2301	HR	95% CI	p value
Any reason	859	675	0.74	0.67; 0.82	<0.001
Atrial Fibrillation	510	335	0.63	0.55; 0.72	<0.001
CHF	132	112	0.86	0.67; 1.10	0.22
ACS	89	62	0.70	0.51; 0.97	0.03
Syncope	32	27	0.85	0.51; 1.42	0.54
Ventricular arrhythmia or cardiac arrest	12	13	1.09	0.50; 2.39	0.83

DIONYSOS Primary Endpoint: AF Recurrence or Premature Study Drug Discontinuation

	Dronedarone	Amiodarone
AF recurrence or premature discontinuation	184	141
Recurrence of AF	158	107
Premature study drug discontinuation	26	34

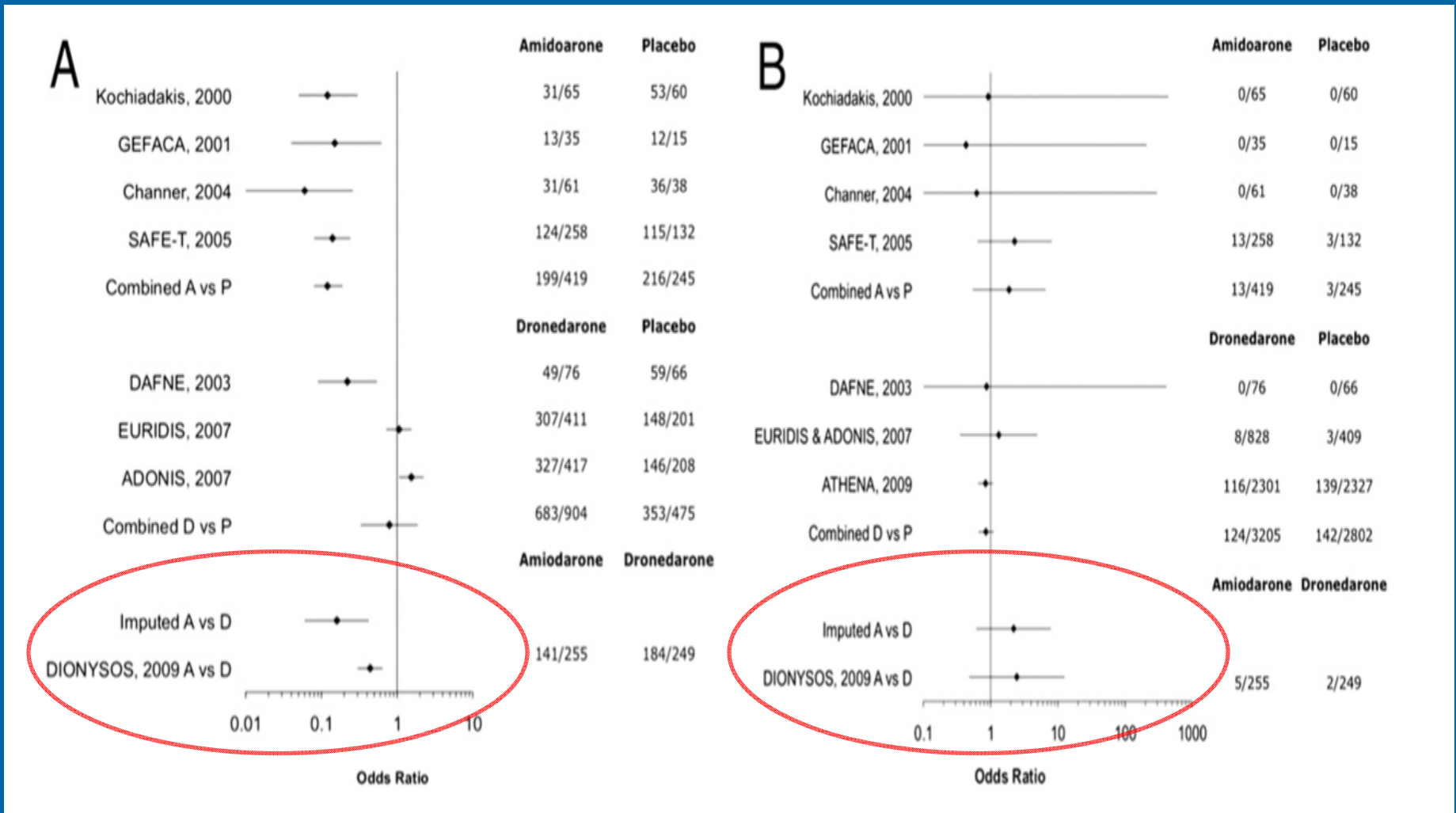


Number at risk

Dronedarone	249	99	84	40	12	0
Amiodarone	255	146	126	61	13	0

Dronedarone and Amiodarone

Treatment Effect Estimates for Amio and Dro



The plots demonstrate odds ratios for (A) recurrent AF, (B) all-cause death

ΑΑ παράγοντες με εκλεκτική δράση στους κόλπους

Atrial repolarization delaying agents (ARDA)

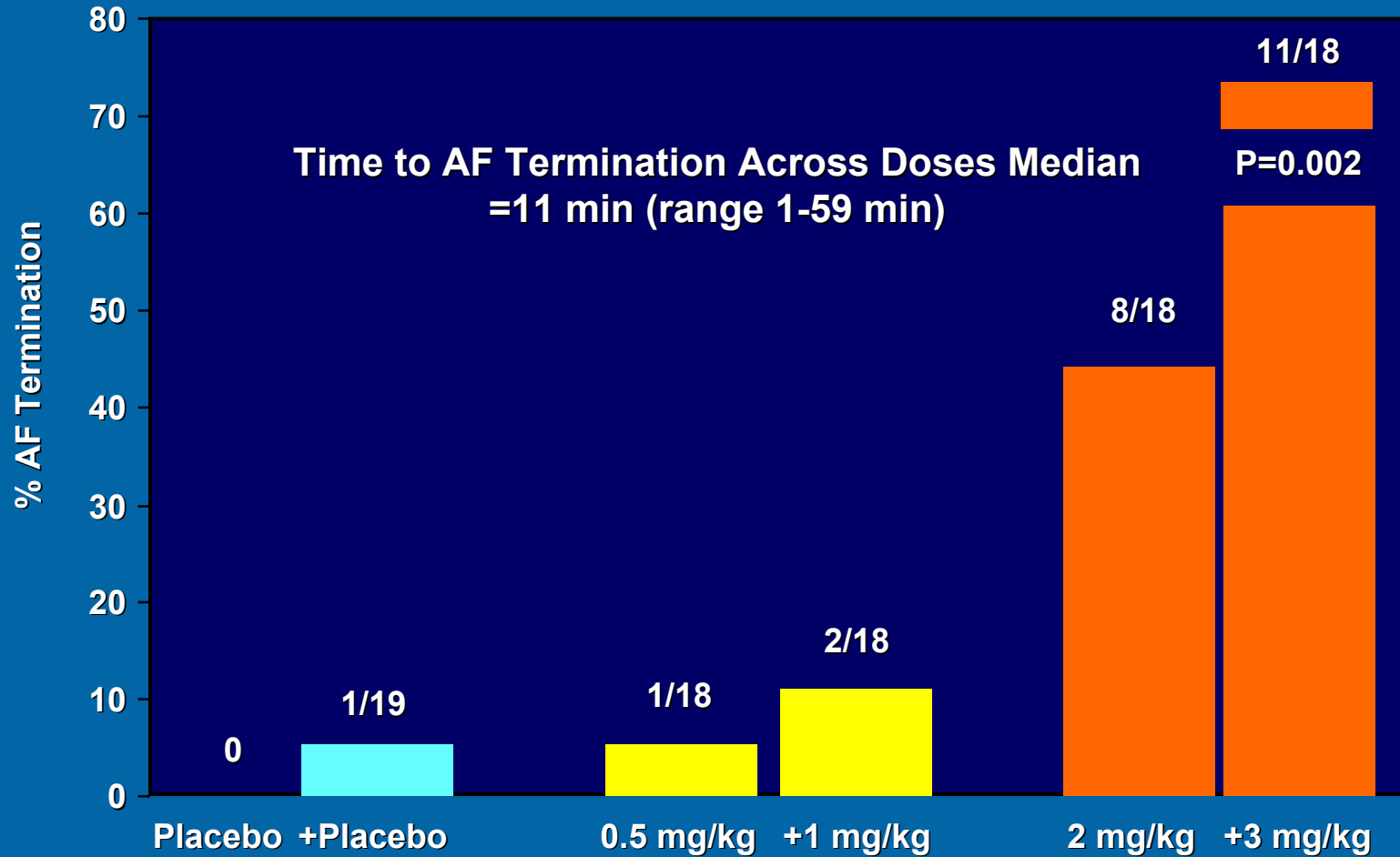
- Αναστέλλουν κυρίως διαύλους ιόντων που καθορίζουν την επαναπόλωση του κοιλιακού μυοκαρδίου
- Αποφεύγεται έτσι η εμφάνιση προαρρυθμίας από τις κοιλίες
 - I_{kur} : επαναπόλωση κόλπων
 - I_{kACh} : καρδιακή συχνότητα, επαναπόλωση κόλπων
 - I_{Na} : επιβραδύνει τα κύματα επανεισόδου (rotors) στην κΜ

ΑΑ παράγοντες με εκλεκτική δράση στους κόλπους

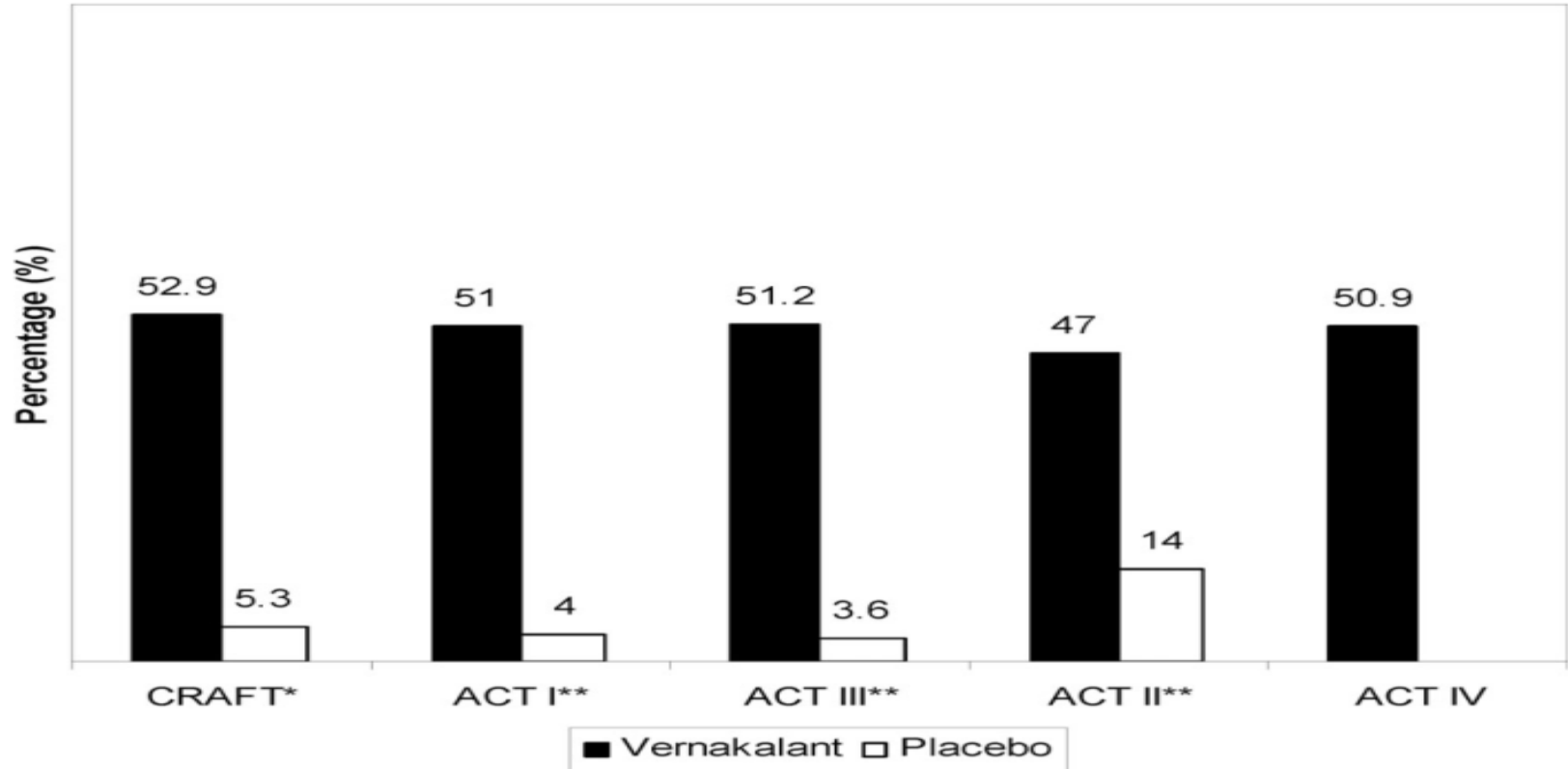
Atrial repolarization delaying agents (ARDA)

- RSD 1235 (Vernakalant) : I_{kur} , I_{to} , $I_{Na,late}$
- AZD 7009 : I_{kur} , I_{to} , I_{kr} , I_{ks}
- AVE 0118 : I_{kur} , I_{to}

RSD 1235 – Vernakalant for Conversion of AF (Phase II dose finding study)



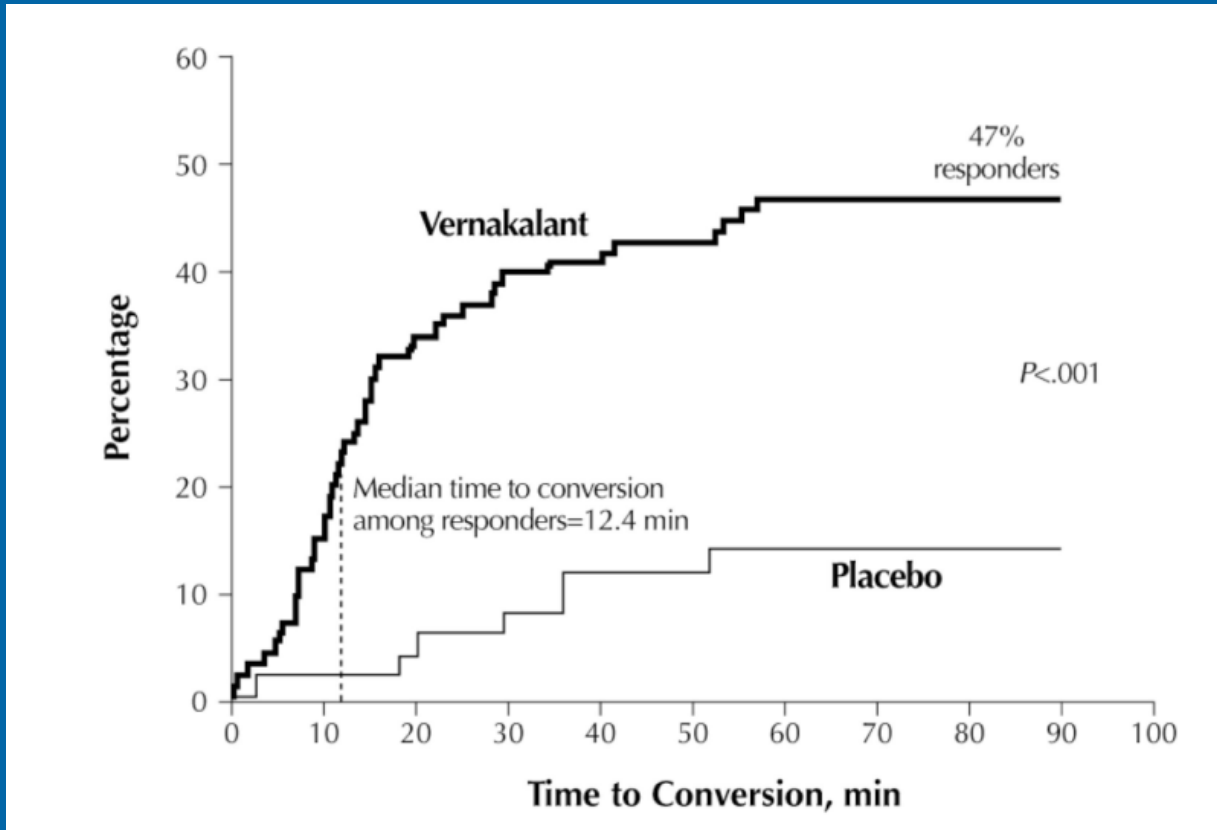
Vernakalant



Vernakalant for conversion of AF to normal SR.

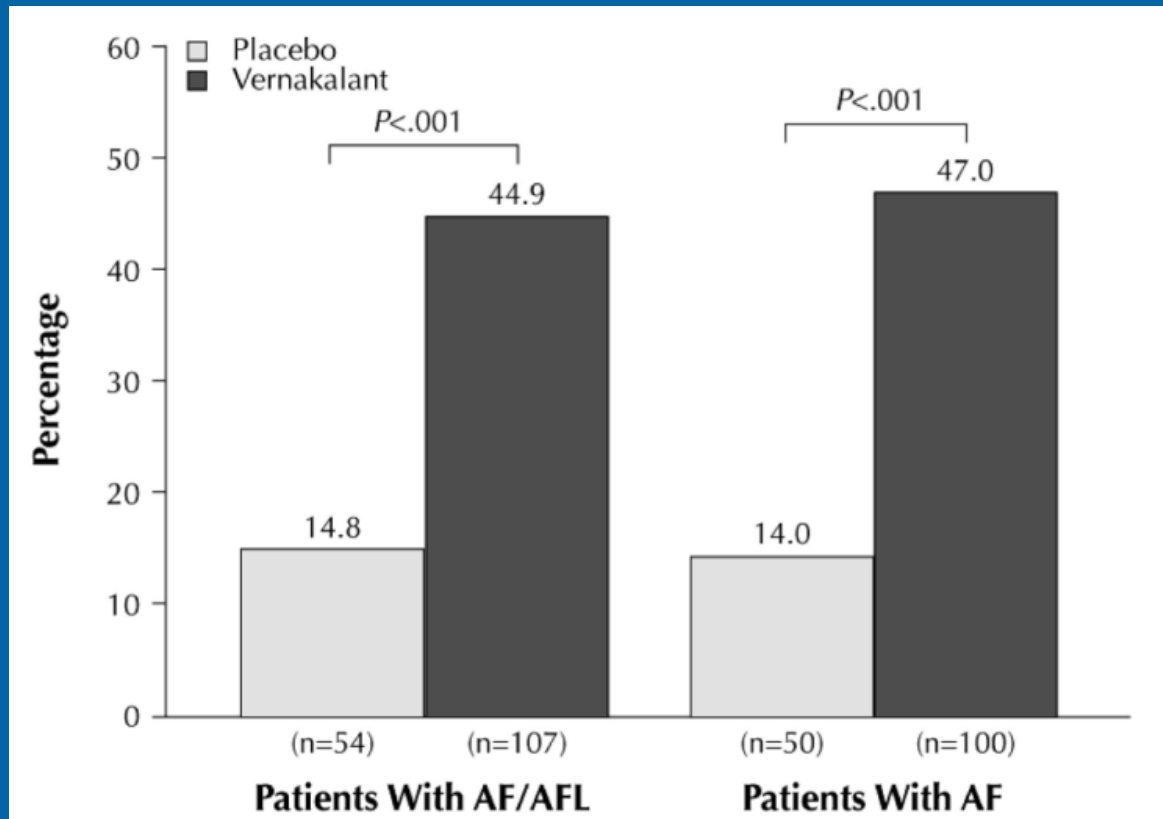
*** $p = 0,0015$, ** $p \leq 0,001$**

Vernakalant in Post-Cardiac Surgery Arrhythmia



Cumulative responder percentage based on time after the start of treatment among patients with AF

Vernakalant in Post-Cardiac Surgery Arrhythmia



Success rates in overall AF/AFL population and among patients with AF

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Τα διαθέσιμα ΑΑ φάρμακα για τη θεραπεία της κοιλιακής μαρμαρυγής έχουν περιορισμένη αποτελεσματικότητα, ενώ η χορήγησή τους περιορίζεται από την εμφάνιση προαρρυθμίας και τοξικότητας.
- Αρκετοί νέοι ΑΑ παράγοντες βρίσκονται υπό έρευνα. Η νεώτερη γενιά ΑΑ παραγόντων περιλαμβάνει, είτε αναστολείς πολλαπλών διαύλων ιόντων (class III), είτε ΑΑ παράγοντες με εκλεκτική δράση στο κοιλιακό μυοκάρδιο (ARDA), με ενθαρρυντικά αποτελέσματα κυρίως όσον αφορά την ασφάλεια και την ανοχή.

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Η δρονεδαρόνη (αναστολέας πολλαπλών διαύλων ιόντων- Class III), είναι αποτελεσματική για τη διατήρηση του φλεβοκομβικού ρυθμού σε ασθενείς με κΜ, αλλά λιγότερο αποτελεσματική από την αμιωδαρόνη.
- Σε ασθενείς με κΜ και παράγοντες κινδύνου η δρονεδαρόνη φαίνεται, ότι μειώνει την καρδιαγγειακή θνητότητα και τις νοσηλείες.
- Ο συνδυασμός ασφαλούς συνταγογράφησης και ασφαλέστερων ΑΑ αποτελεί σημαντικό παράγοντα για τη φαρμακευτική θεραπεία της κΜ.