

Ambassadors Hotel, London  
February 11<sup>th</sup> 2009



# Atrial Fibrillation New Developments in Treatment

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United Kingdom



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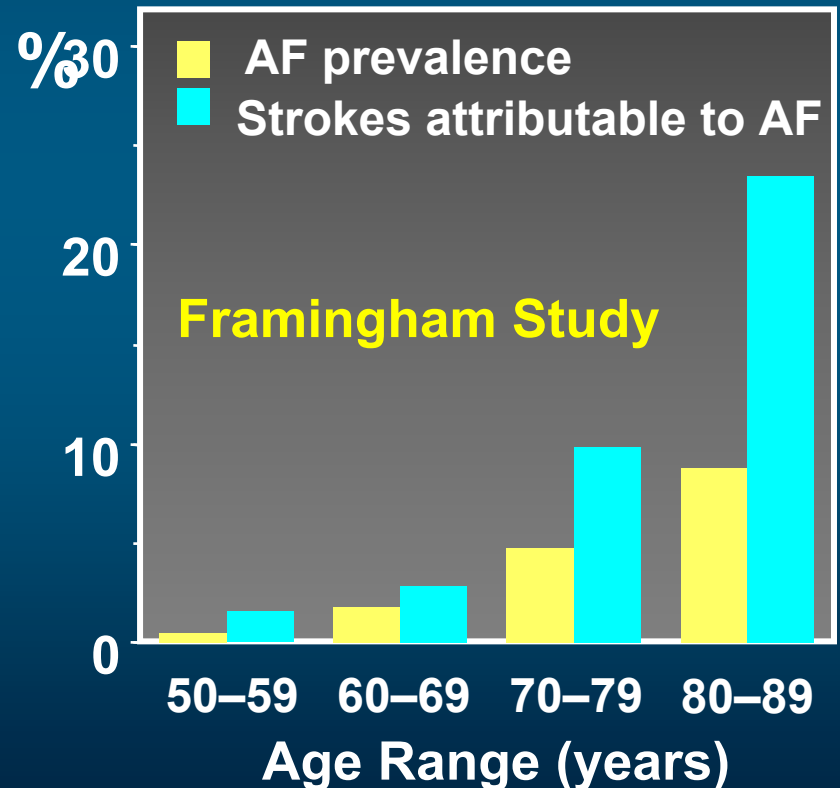
## Conflicts of Interest

Advisor / Speaker : [sanofi aventis](#), Astra Zeneca, Cardiome,  
Astellas, Xention, ARYx, Prism, Bristol Meyer Squibb, Daiichi,  
[Merck](#), Medtronic, St. Jude, [Boehringer Ingleheim](#), Boston  
Scientific

# Risk of Stroke in Atrial Fibrillation

Placebo Stroke Rate – 4.5%/yr  
1 of 6 strokes attributable to AF

- Previous stroke/TIA 2.5
- History of hypertension 1.6
- Advanced age (continuous) 1.4/10 yr
- Diabetes mellitus 1.7
- History of CHF 1.4



Collaborative Analysis—AFib Investigators.  
*Arch Intern Med.* 1994;154:1449-1457.

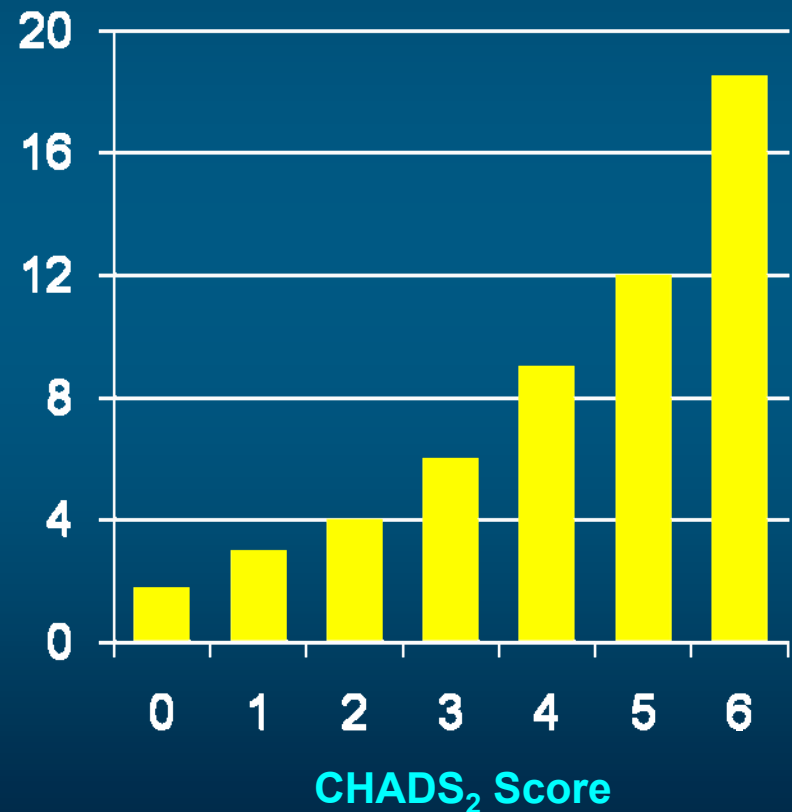
Wolf et al. *Stroke* 1991;22:983-988.

# Atrial Fibrillation

## Stratification of stroke risk: CHADS<sub>2</sub> score

	Score
CHF or LV dysfunction	1
Hypertension	1
Age > 75 years	1
Diabetes	1
Stroke/TIA	2

Adjusted Stroke Rate (per 100 pt years)



# Antithrombotics in Atrial Fibrillation

CHADS <sub>2</sub> Score	Situation	Recommendation
0	No risk known risk factors	None or aspirin
1	One moderate RF (age > 75, HF (or LVEF < 35%), hypertension (?LVH), diabetes mellitus)	Aspirin or warfarin
≥ 2	More than one moderate RFs	Warfarin

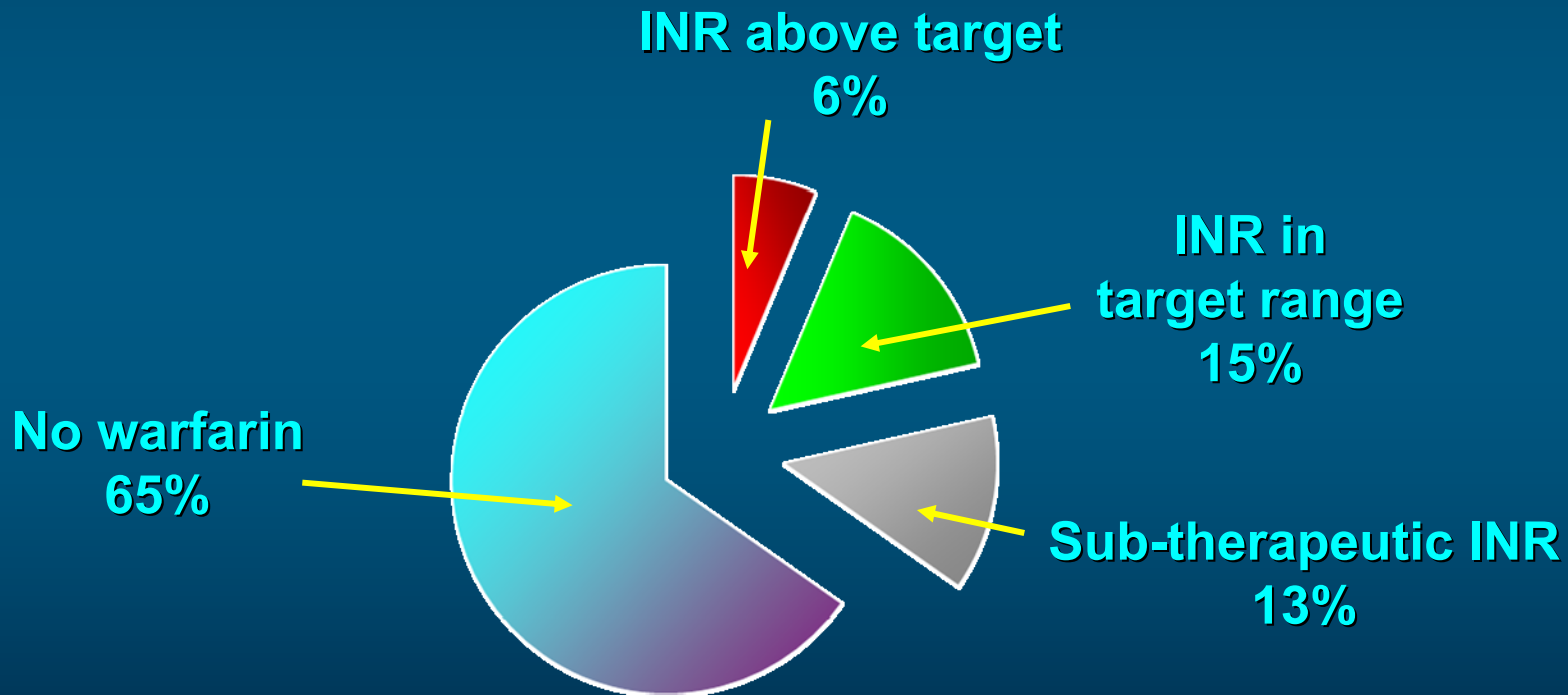
**High Risk factors: rheumatic mitral stenosis, previous thromboembolism**

**Less well validated risk factors = age 65-74 years, coronary artery disease, thyrotoxic basis, female gender**

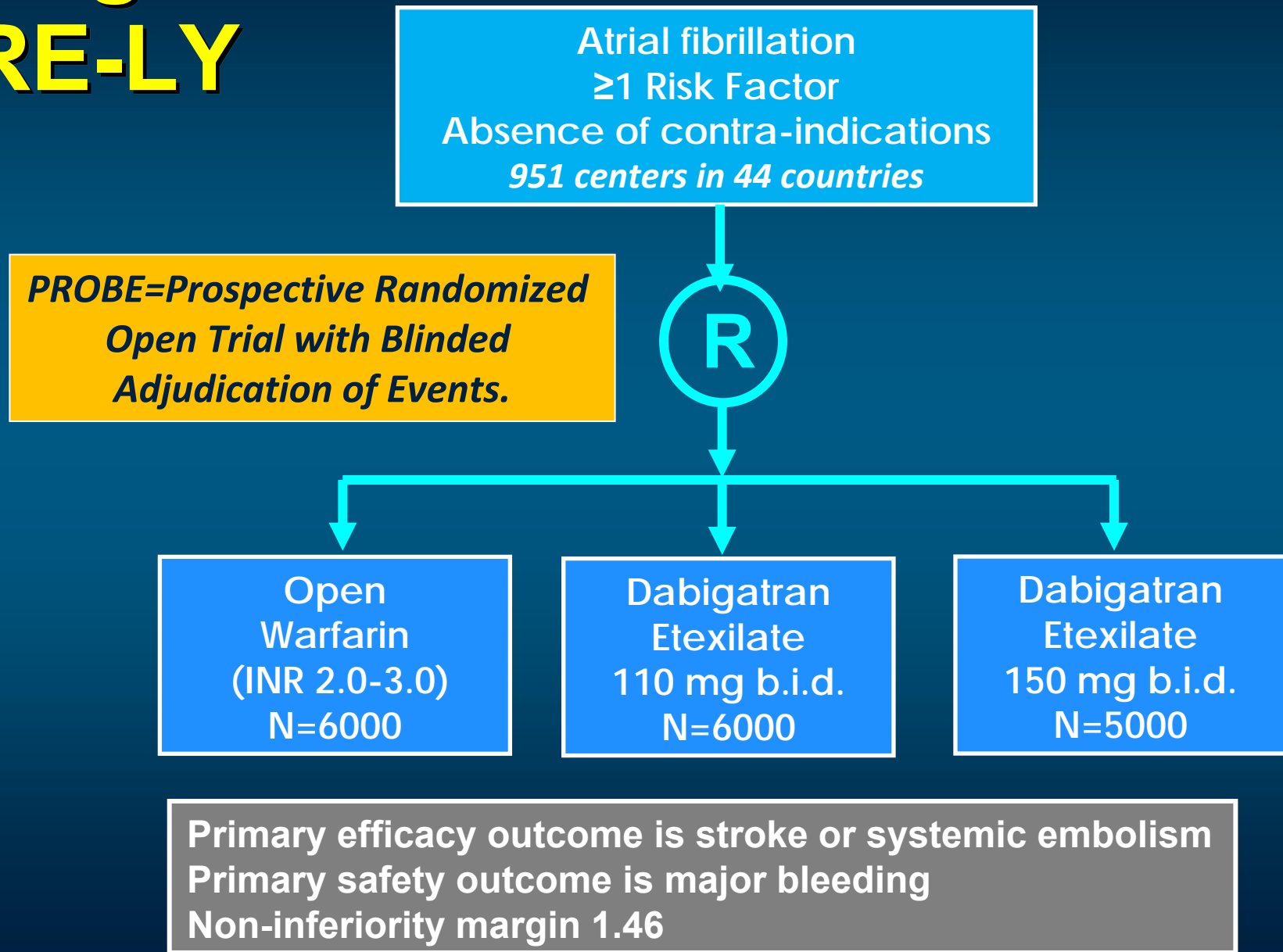
**Other factors: peripheral vascular disease, chronic renal failure**

# Inadequate VKA Treatment for AF

## Adequacy of Anticoagulation in Patients with AF in Primary Care Practice



# Design of RE-LY



Atrial fibrillation  
≥1 Risk Factor  
Absence of contra-indications  
*951 centers in 44 countries*



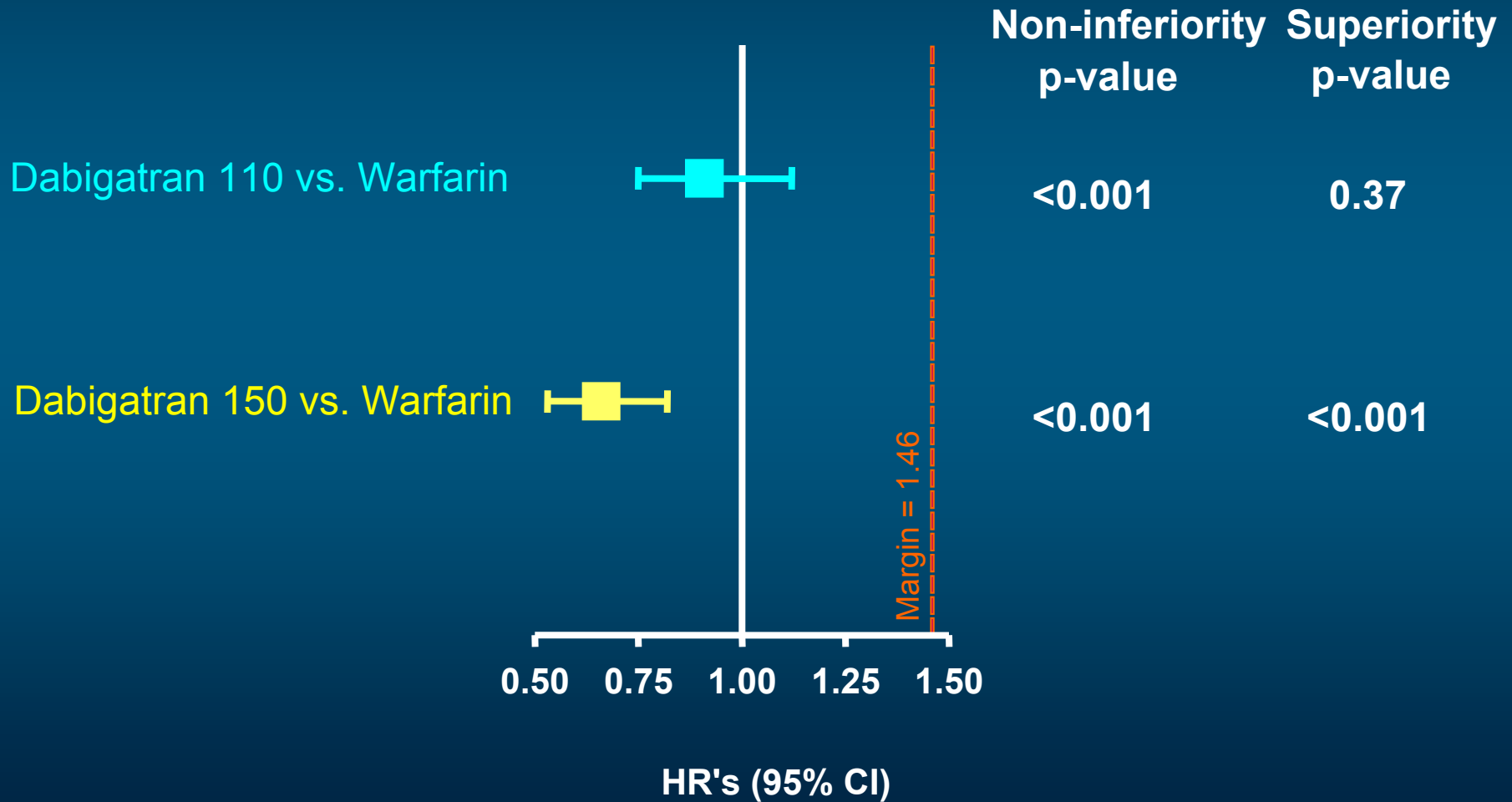
Open Warfarin  
(INR 2.0-3.0)  
N=6000

Dabigatran Etexilate  
110 mg b.i.d.  
N=6000

Dabigatran Etexilate  
150 mg b.i.d.  
N=5000

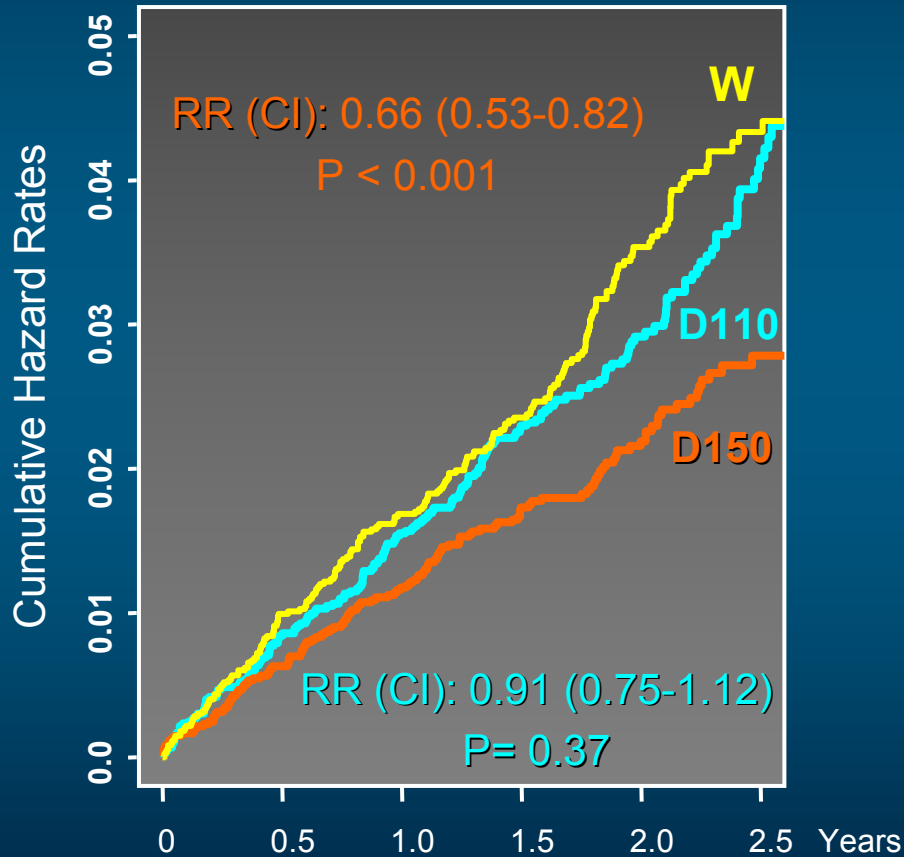
Primary efficacy outcome is stroke or systemic embolism  
Primary safety outcome is major bleeding  
Non-inferiority margin 1.46

# Stroke and Systemic Embolism

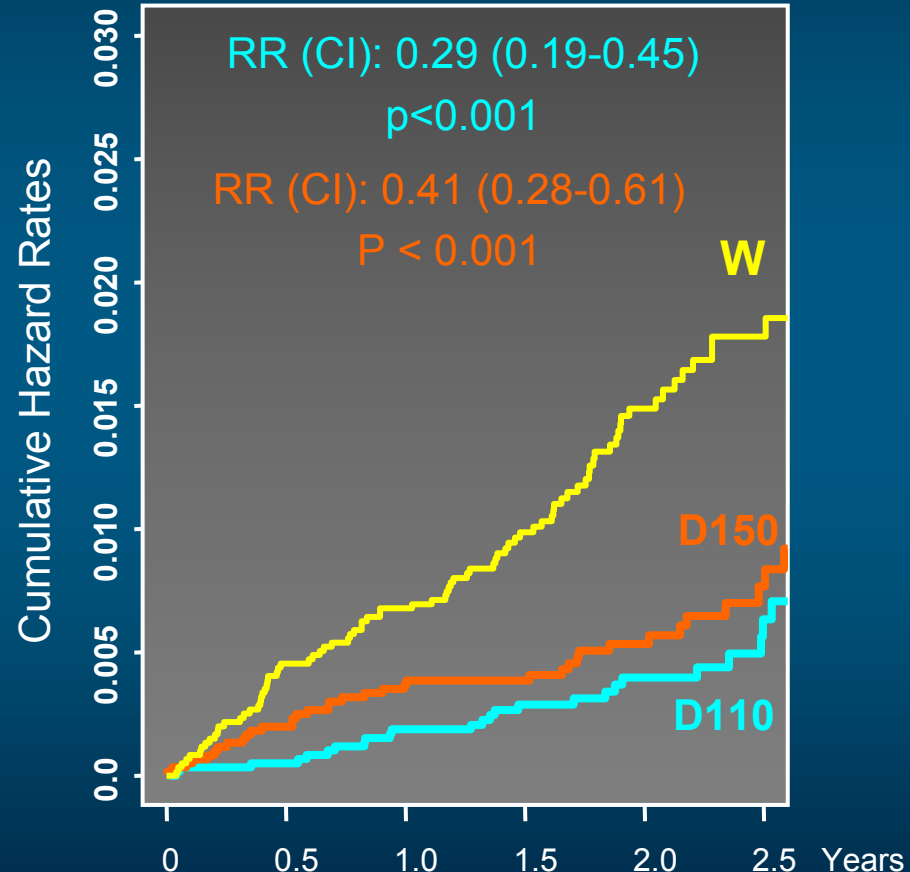


# The RE-LY Trial

## Primary Outcome

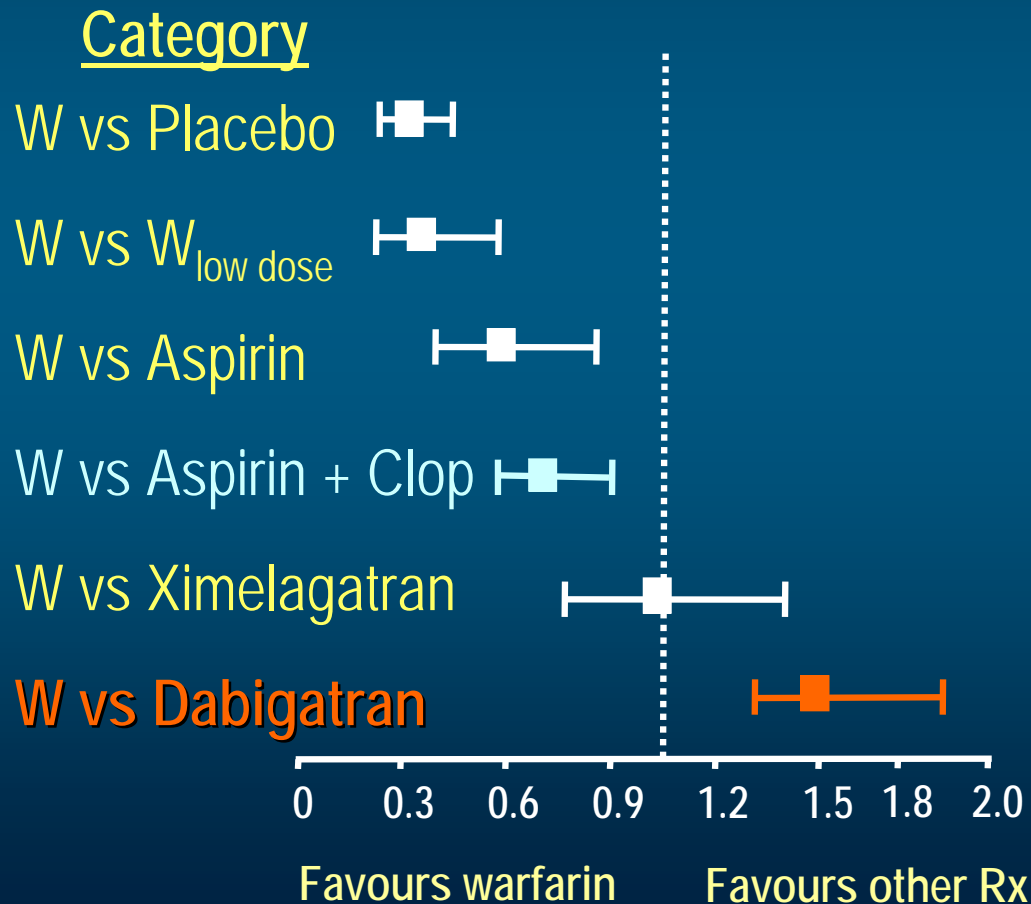


## Intracranial Haemorrhage



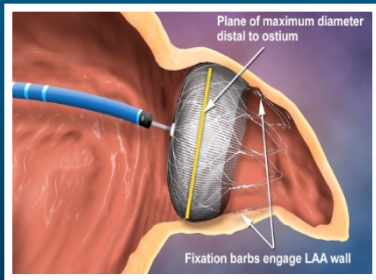
# Stroke Prevention: *Dabigatran*

Meta-analysis of ischaemic stroke or systemic embolism

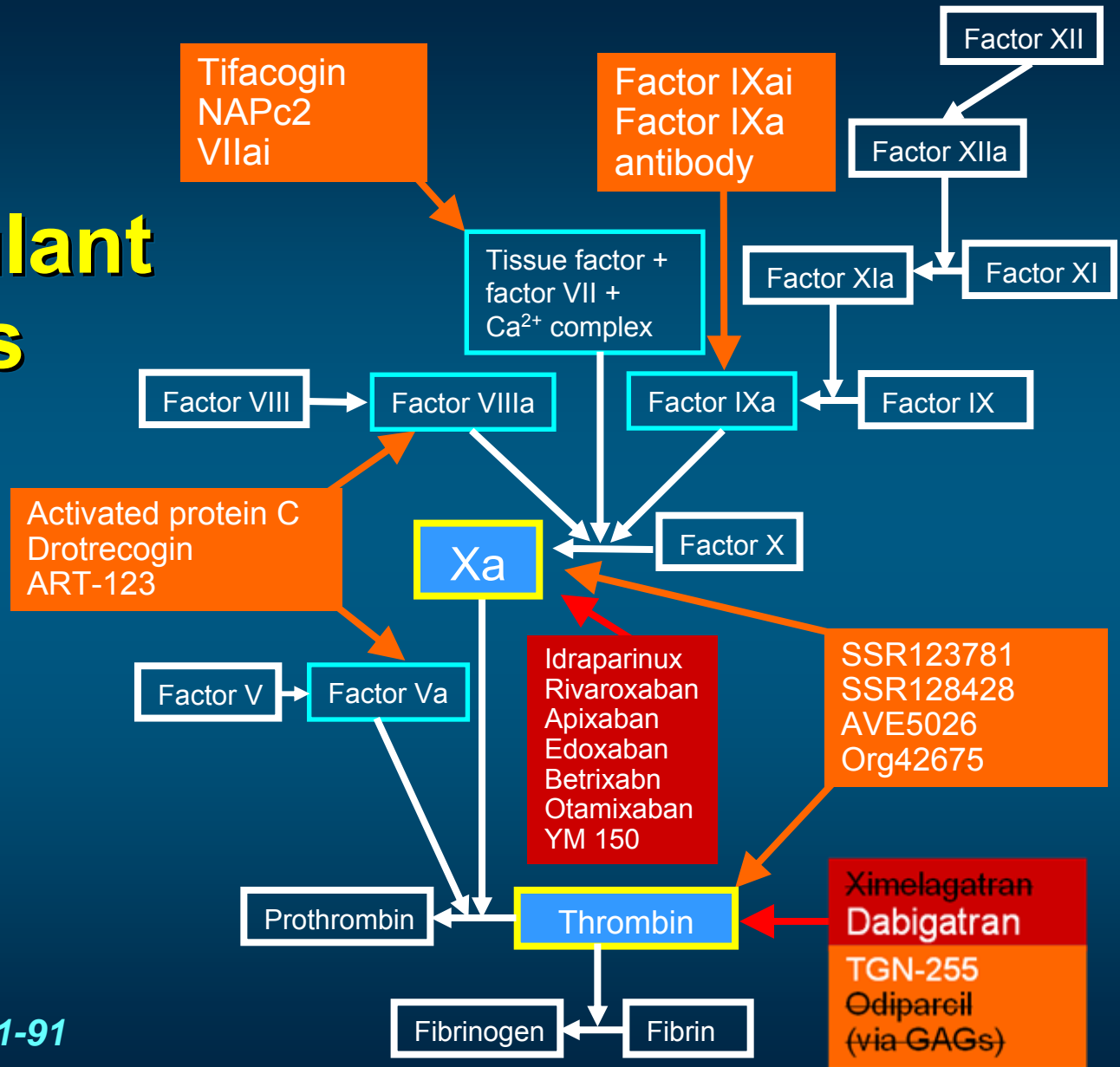


# New Anticoagulant Targets

## Tercafarin



Savelieva I, et al.  
Ann Med 2007;39:371-91

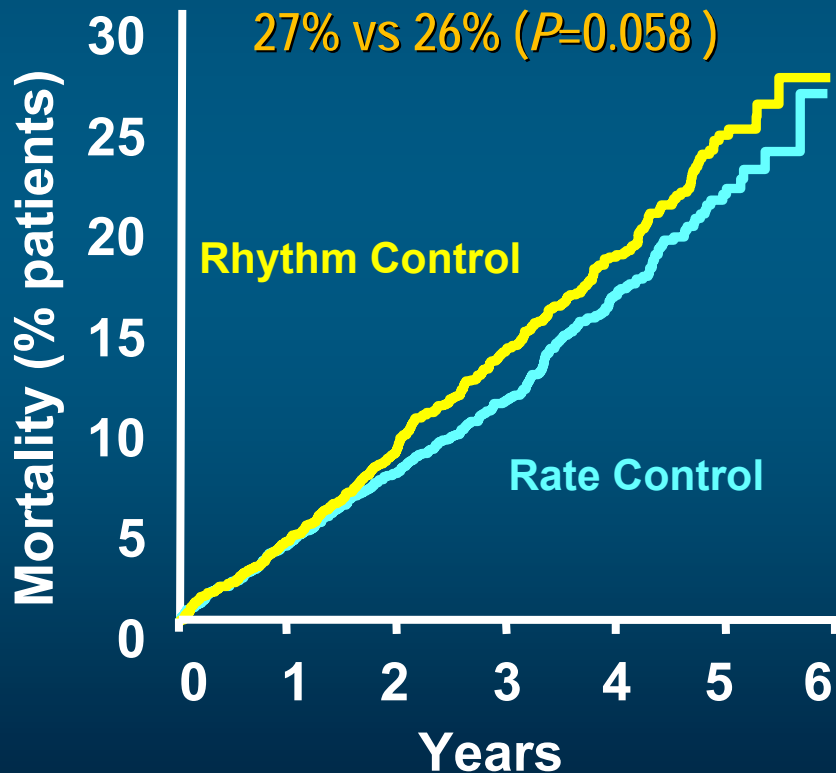


# AFFIRM : Main Results

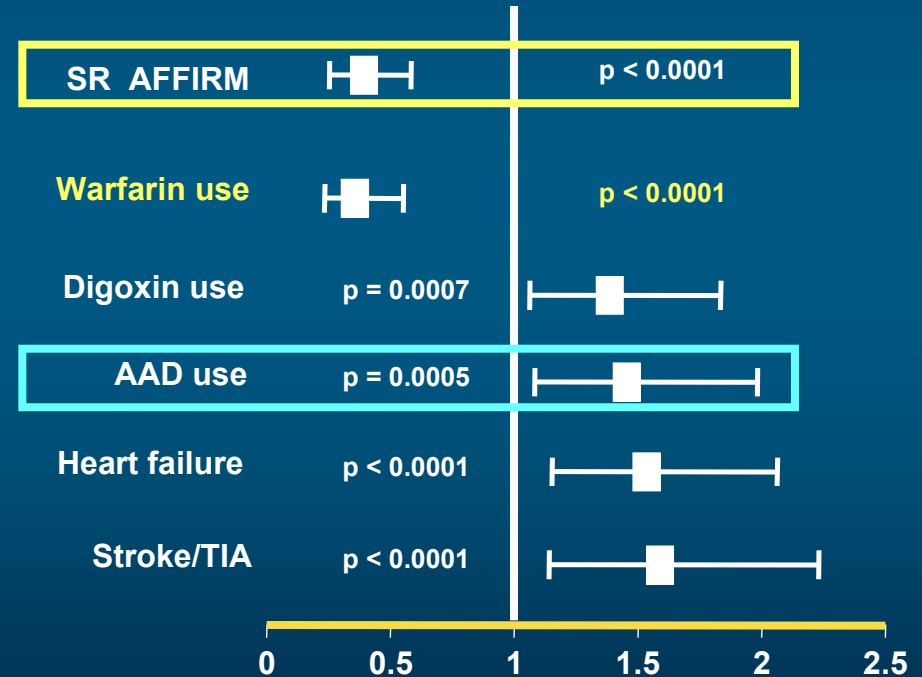
## AFFIRM

All-cause Death

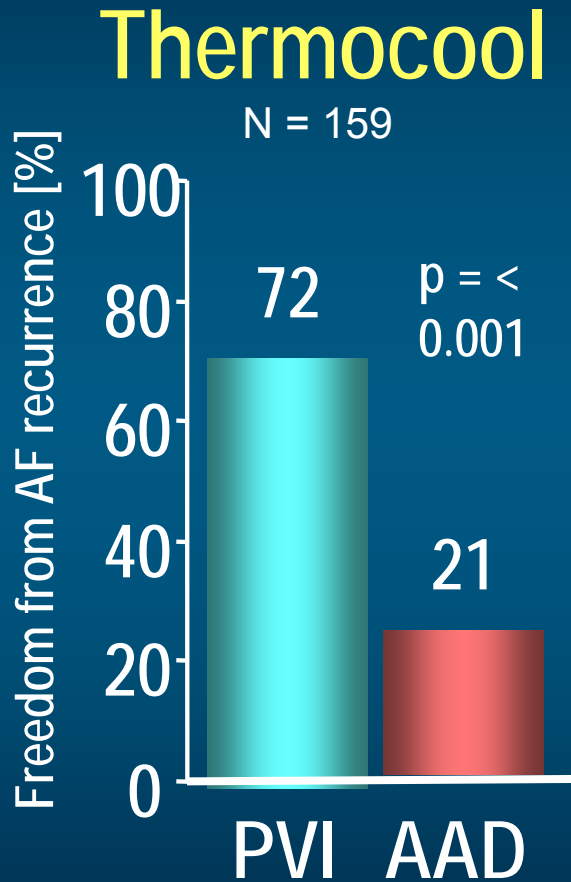
27% vs 26% ( $P=0.058$ )



## Hazard Ratio



# AF Ablation or Antiarrhythmic Drugs?



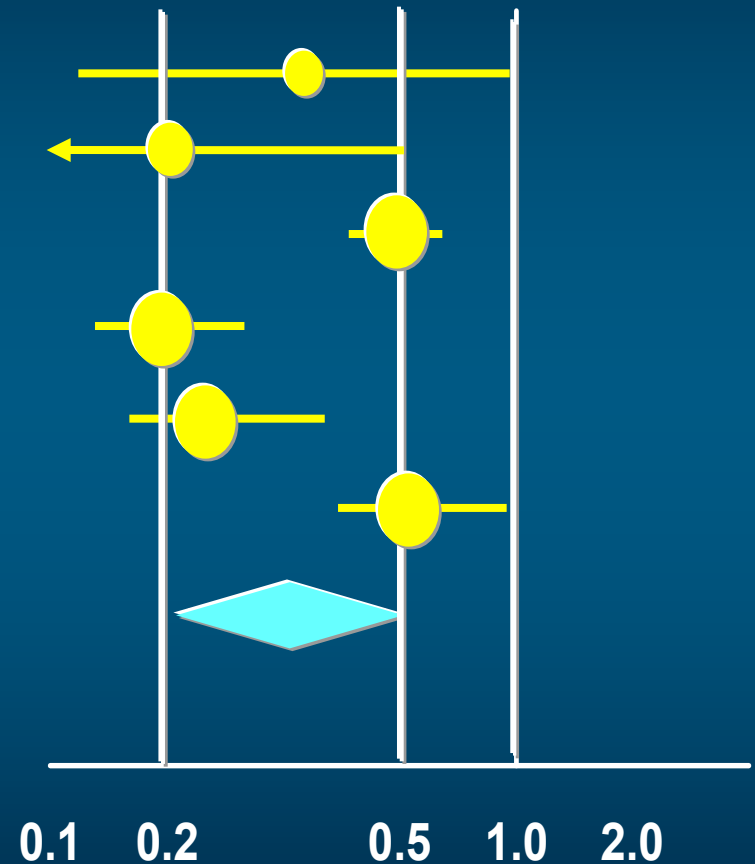
Wilber D et al, JAMA, 2009

Study	No. of patients	Previous use of AAD	Crossed over to ablation	Patients without AF, %
				Ablation vs AAD or no AAD
Jais et al, 2008 (A4 study)	112	$\geq 1$ AAD failure	63%	89 vs 23
Krittayaphong et al, 2003	30	$\geq 1$ AAD failure <sup>d</sup>	Not stated	79 vs 40
Wazni et al, 2005 (RAAFT)	70	No	49%	87 vs 37
Stabile et al, 2006 (CACAF)	137	$\geq 1$ AAD failure	57%	56 vs 9
Oral et al, 2006	146	$\geq 1$ AAD failure (mean $2.1 \pm 1.2$ )	77%	74 vs 4
Pappone et al, 2006 (APAF)	198	$\geq 2$ AAD failure (mean $2 \pm 1$ )	42%	86 vs 22
Forleo et al, 2008	70	$\geq 1$ AAD failure	Not stated	80 vs 43

Camm J and Savelieva I, Nature CV Reviews, 2009

# RCTs of Ablation Versus AADs in AF

Thai study	0.333	0.1120.9950.049
RAAFT	0.204	0.0780.5310.001
CACAF	0.483	0.3660.6380.000
APAF	0.187	0.1130.3070.000
A4	0.258	0.1510.4150.000
Morady	0.618	0.3870.9870.044
Total	0.331	0.2170.5050.000



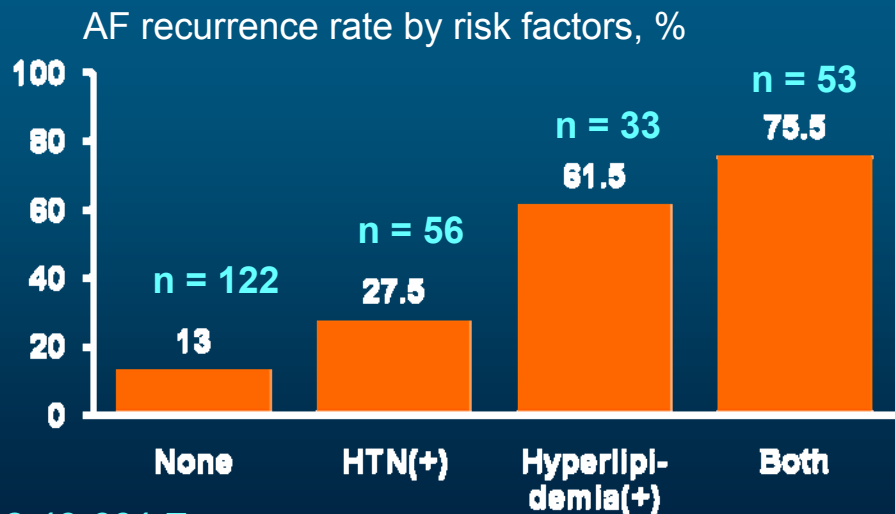
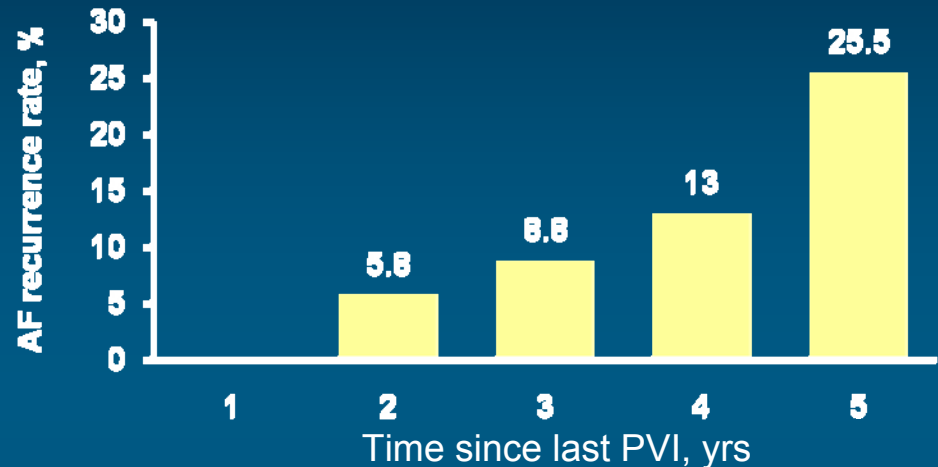
“Inclusion of case series can increase the evidence base and strengthen the credibility of a review of an emerging health technology”

Chambers D, et al. *J Clin Epidemiol* 2009

Nair GM, et al. *JCE* 2008

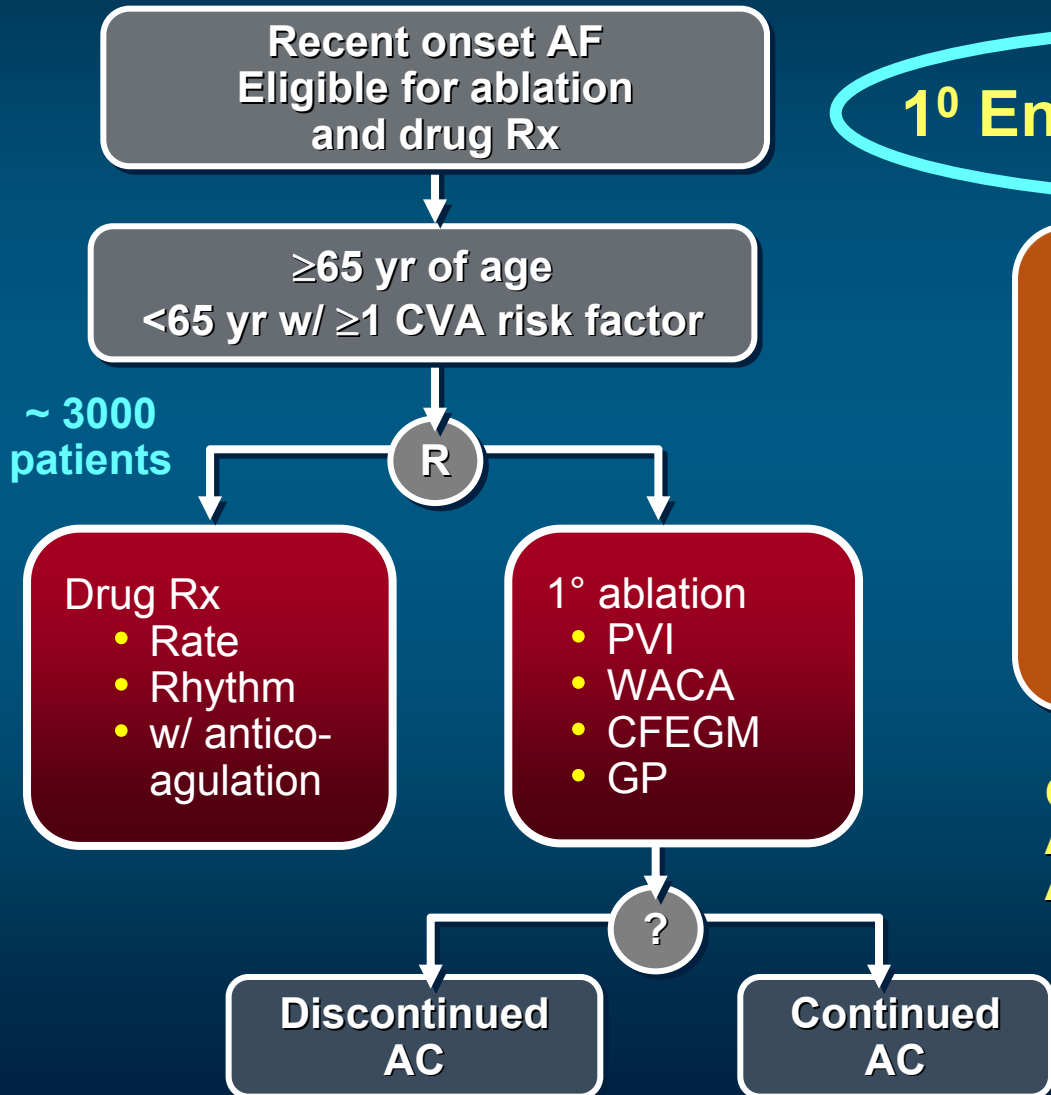
# Long-term Outcome after PVI: Late Recurrence

- n = 264 of 350 without recurrence in year one
- 57 ± 12 yrs
- Follow-up 28 ± 12 months (up to 5 years)
- 23 (8.7%) recurrent AF
- Repeat ablation in 18/23



# CABANA Trial Design

**1<sup>o</sup> Endpoint: total mortality**



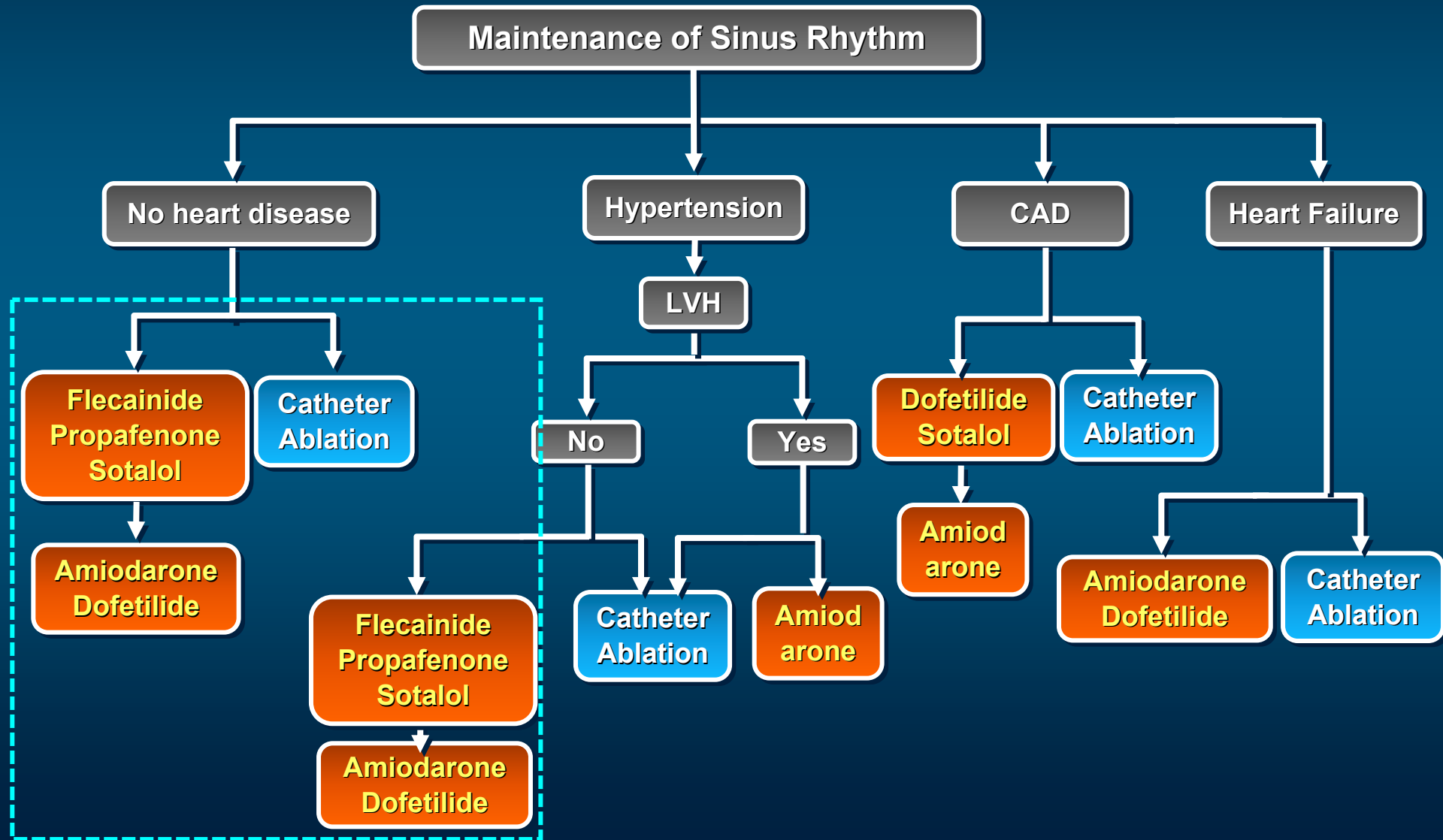
## Secondary analysis

- 1) NSR vs AF
- 2) ± underlying heart disease
- 3) AF type (parox, pers, perm)
- 4) D/C anticoagulation

**Catheter Ablation vs  
Antiarrhythmic Drug Therapy for  
Atrial Fibrillation**

*After Douglas Packer*

# Potential AF Guideline Revision '10/11



# Antiarrhythmic Medical Therapies

Class Ia: Disopyramide, Quinidine and Procainamide

**Beta Blocker**  
Antiarrhythmic Agents  
New and Old

Class III

Class Ic

Amiodarone

Sotalol

Propafenone

Flecainide

Upstream therapies

New Class III Agents

Novel Drugs

Nexterone and Budiodarone

SAC Blockers

Rotigaptide

Abandoned

Abandoned

Ranolazine

Na<sup>+</sup>/H<sup>+</sup> Inhibitor

Abandoned

Dronedarone

Na<sup>+</sup>/Ca<sup>2+</sup> Inhibitor

NTC-801

Multi-channel blockers

Vernakalant

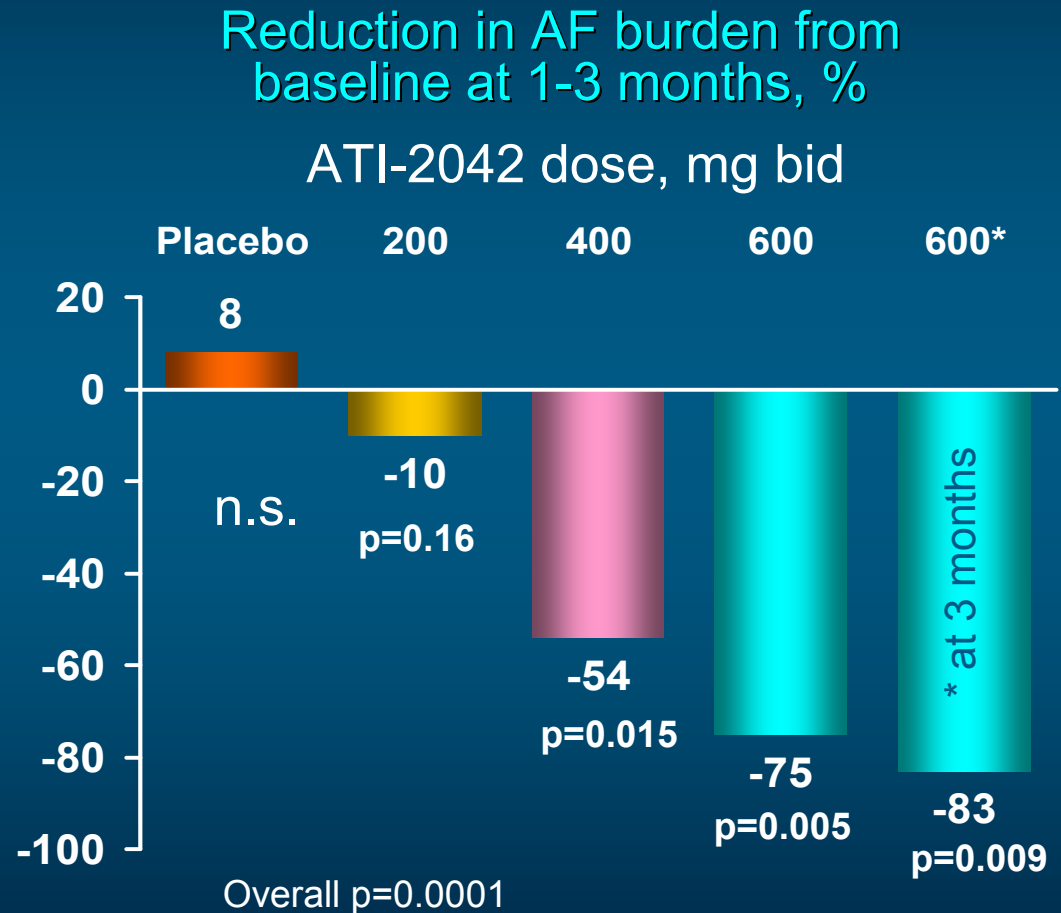
Celivarone

Xen 0101

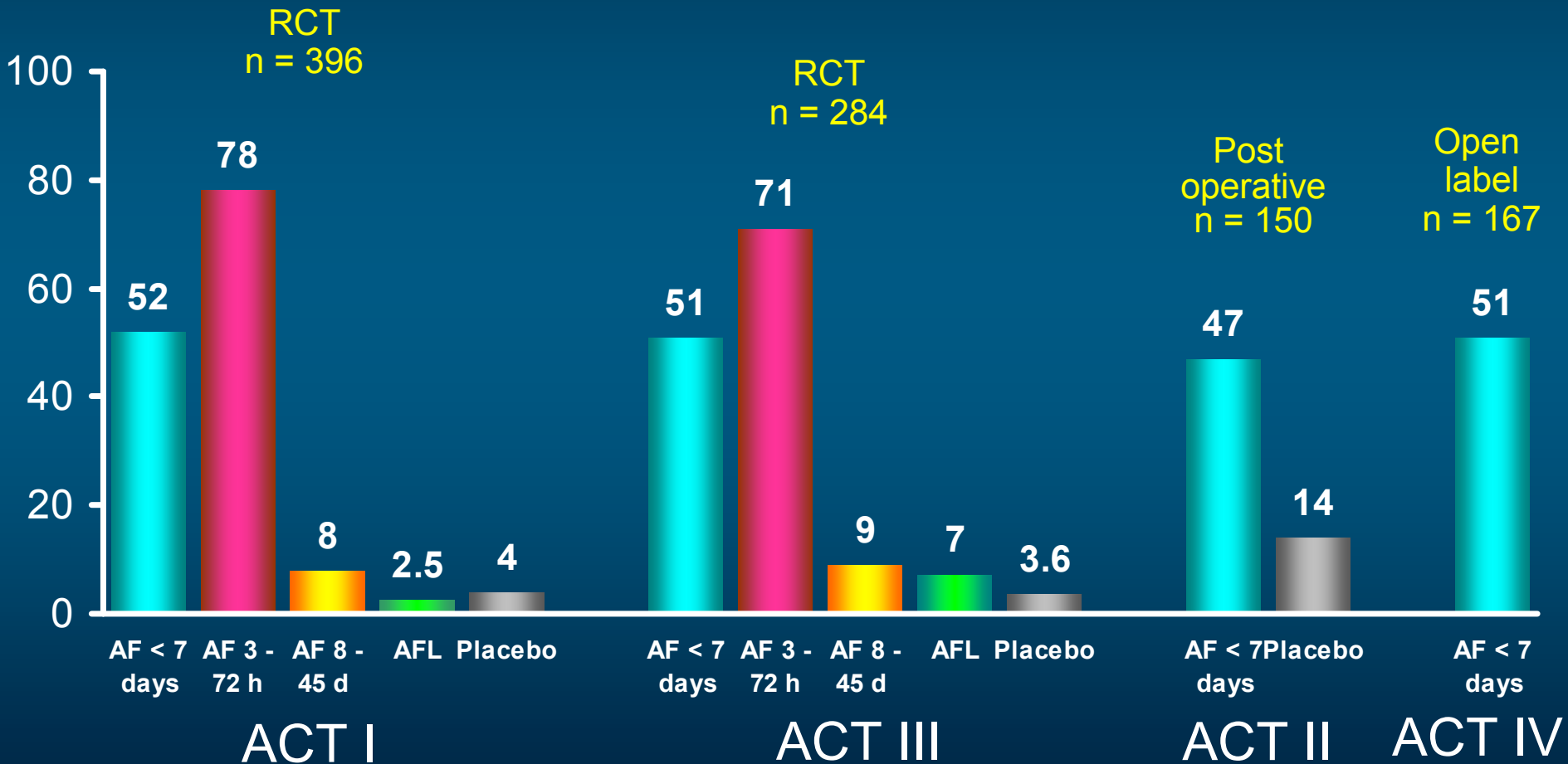
# Efficacy and Safety of Budiodarone

(P)aroxysmal (A)trial fibrillation (S)tudy with (C)ontinuous (A)trial fibrillation (L)ogging

- Degraded to non-active metabolites by serum esterases
- Enhanced safety - metabolism optimized and improved relative to amiodarone
- Significantly shorter biological half-life,  $T_{1/2} = 7$  hrs +
- Avoids safety issues due to organ accumulation

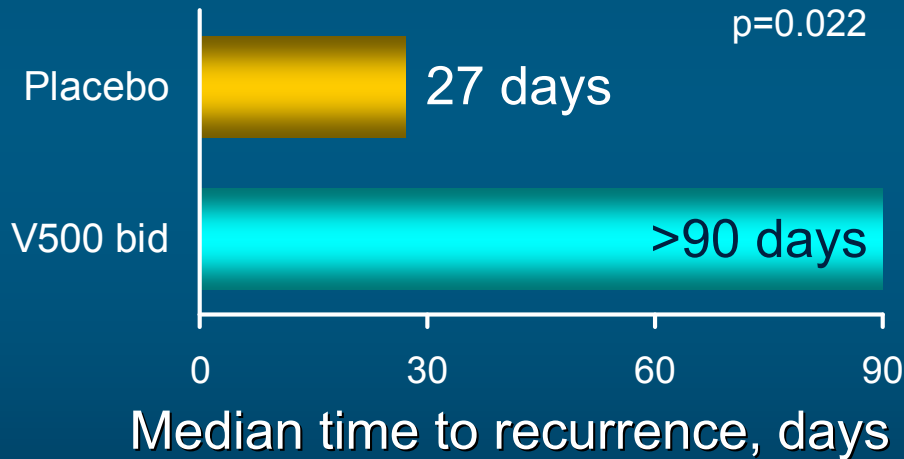


# AF Cardioversion With Vernakalant in ACT (Atrial arrhythmia Conversion Trials) I-IV



# Studies of Oral Vernakalant Phase IIb

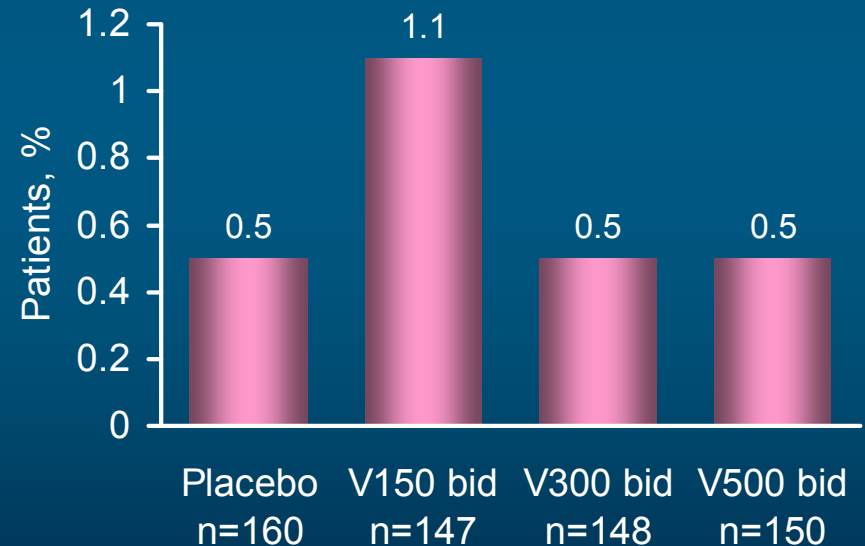
	# patients	Inclusion criteria	Dose	Treatment	Duration
Phase IIb	735; 605 treated	AF 30-180 days	150, 300 or 500 mg bid	3-day load, DCC	> 90 days



In SR V500 vs Placebo: 51% vs 37%

V150 and V300 vs Placebo: n.s.

## Drug-related SAE

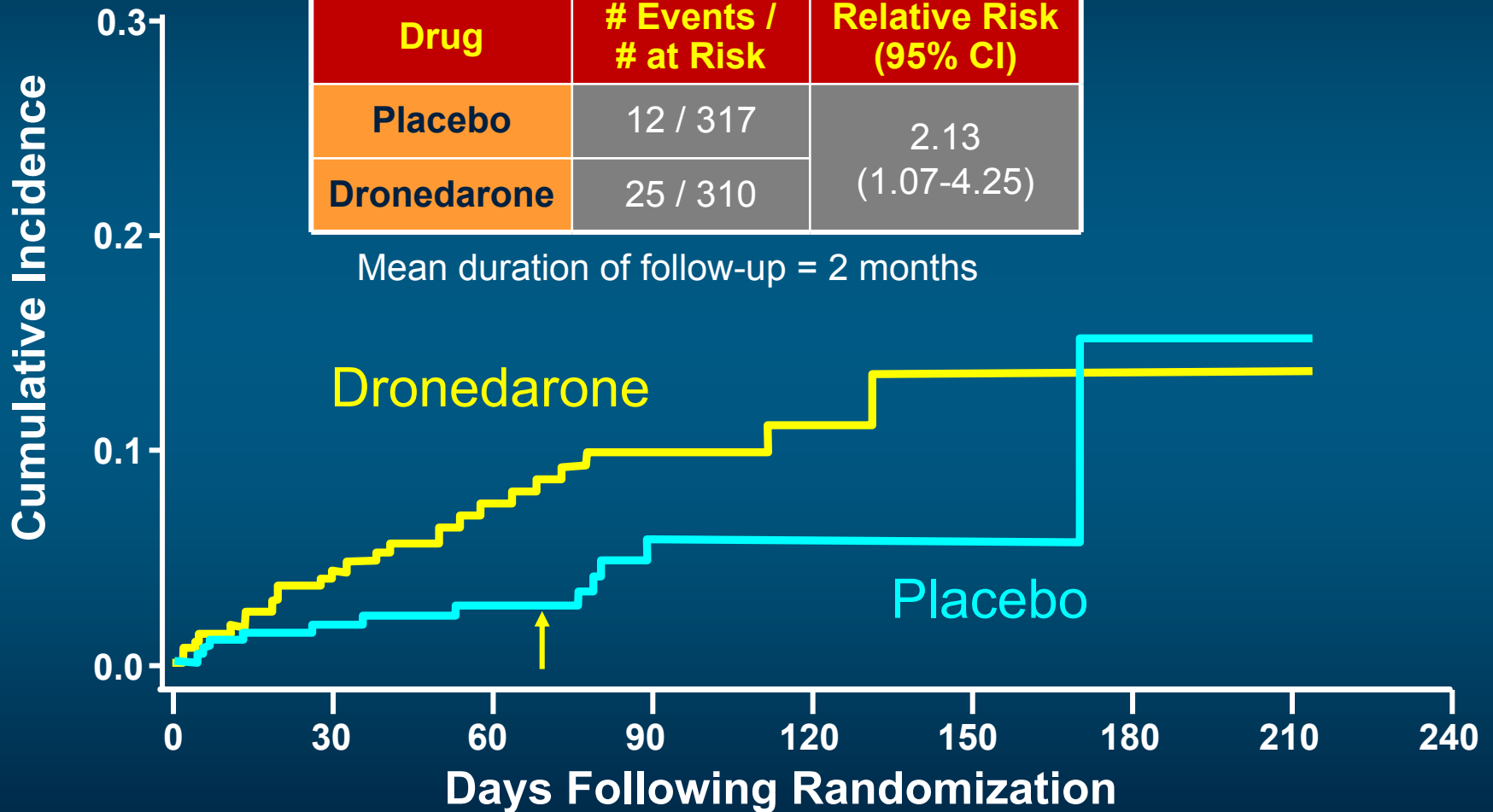


No TdP, Deaths: 2 on placebo, 1 on V150, 1 on V300, 0 on V500 (all not drug-related)

# ANDROMEDA: Mortality Results at Time of DSMB Recommendation

Drug	# Events / # at Risk	Relative Risk (95% CI)
Placebo	12 / 317	2.13 (1.07-4.25)
Dronedarone	25 / 310	

Mean duration of follow-up = 2 months

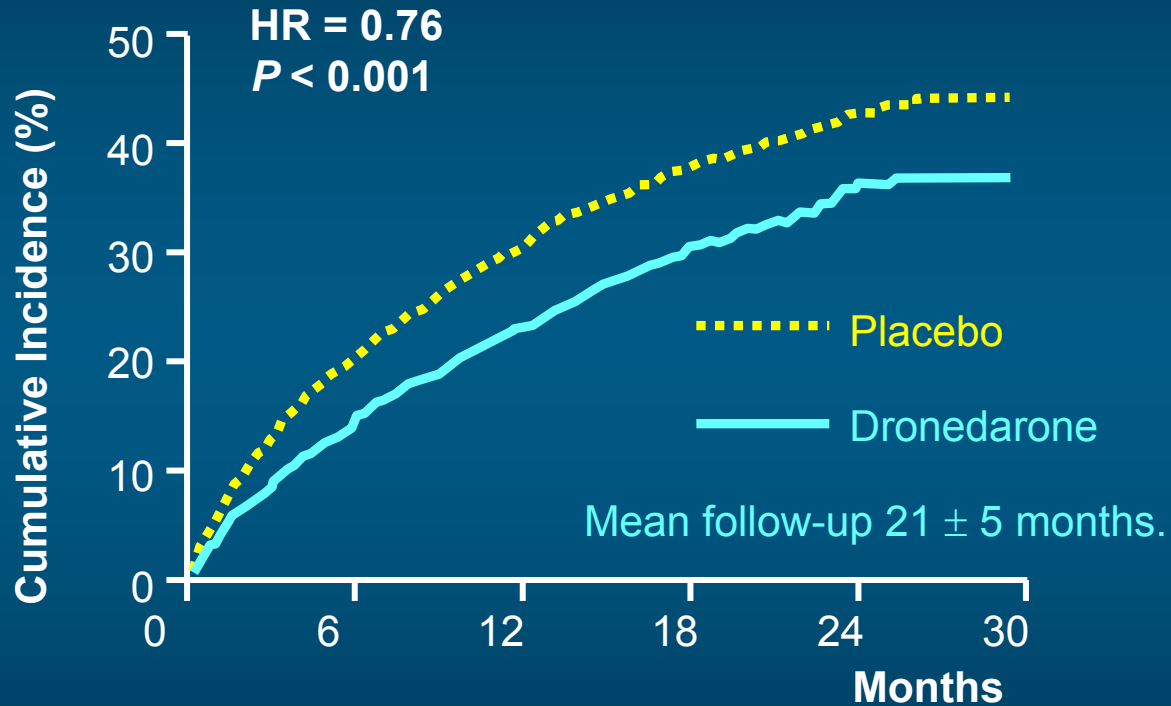


At risk

PBO	317	256	181	103	50	18	6	1
DRO	310	257	174	104	59	22	5	1

# ATHENA: Primary Outcome

Time to first cardiovascular hospitalization or death



Patients at risk

Placebo

2327 1858 1625 1072 385 3

Dronedaron

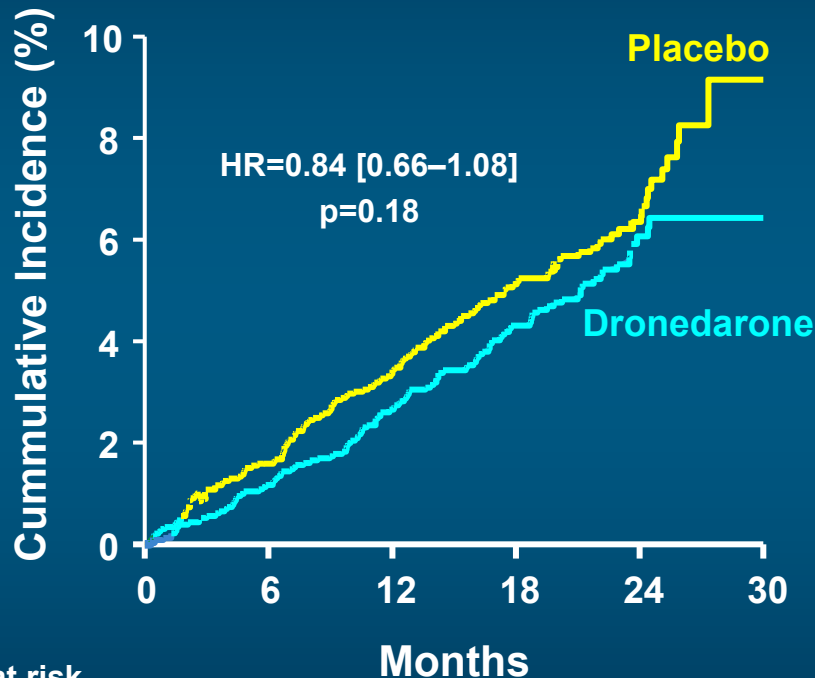
2301 1963 1776 1177 403 2

Hohnloser SH et al. ATHENA Investigators. *N Engl J Med.* 2009 Feb 12;360(7):668-78.

# Total and Cardiovascular Mortality

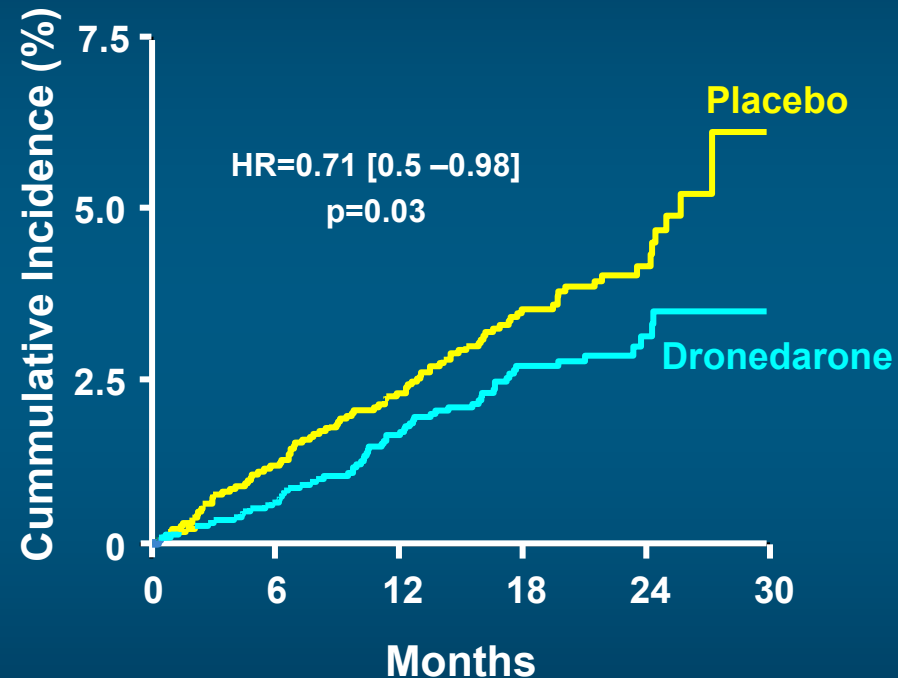
## All Cause Mortality (ACM)

Not statistically significant



## Cardiovascular Mortality

Analysis plan: not assessed if ACM not +ve



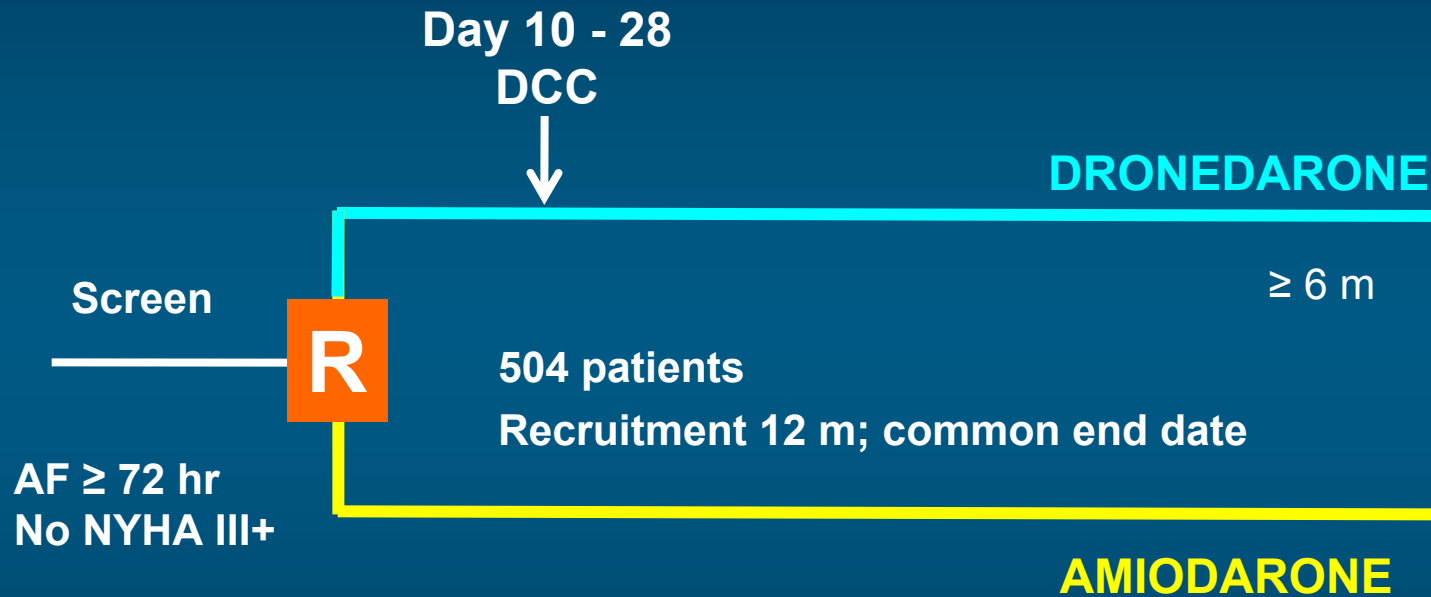
Patients at risk

	0	6	12	18	24	30
Placebo	2327	2290	2250	1629	636	7
Dronedaron	2301	2274	2240	1593	615	4

	0	6	12	18	24	30
Placebo	2327	2290	2250	1629	636	7
Dronedaron	2301	2274	2240	1593	615	4

Mean follow-up 21±5 months

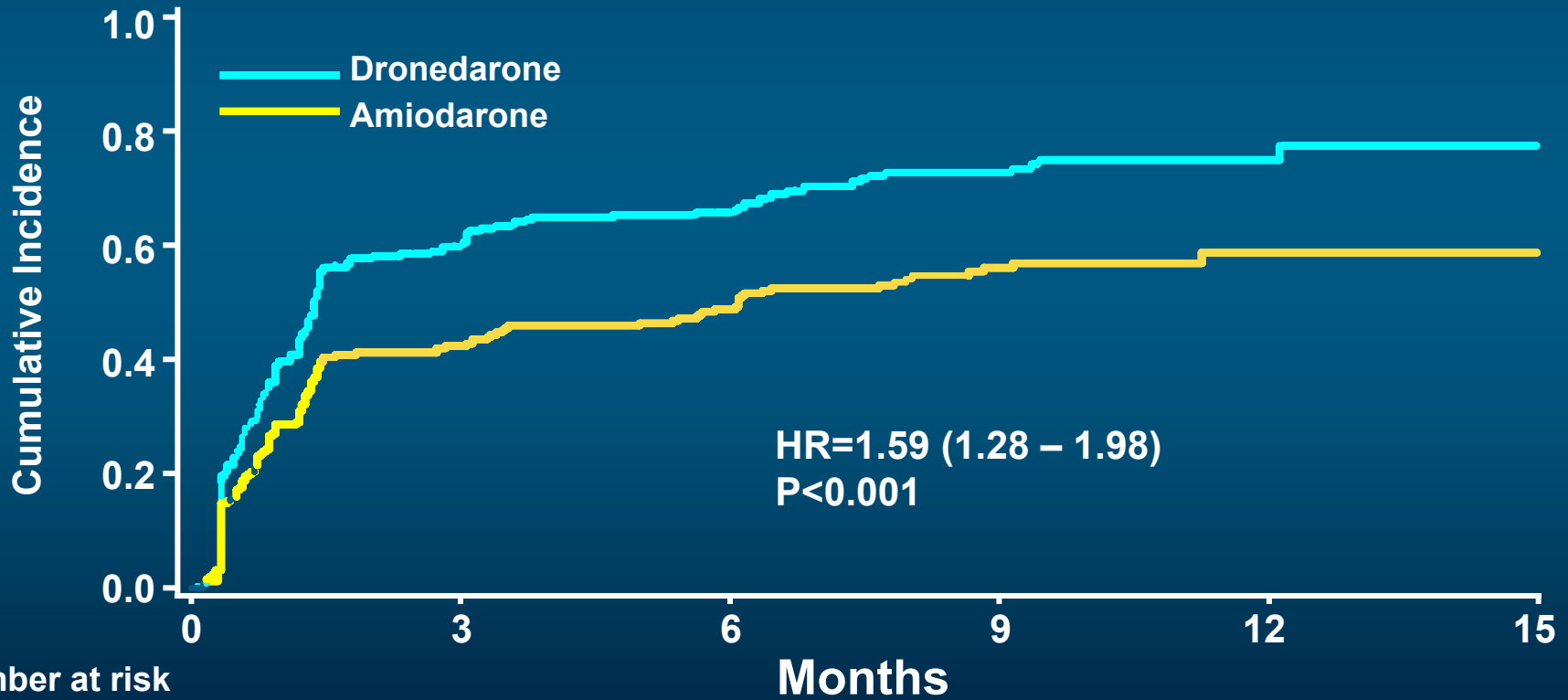
# Dronedarone - DIONYSOS



- 1<sup>0</sup> Endpoint: Time to AF recurrence or drug discontinuation
- 2<sup>0</sup> Endpoint: Components of 1<sup>0</sup> endpoint  
Time to development of adverse event

# DIONYSOS Primary Endpoint: AF Recurrence or Premature Study Drug Discontinuation

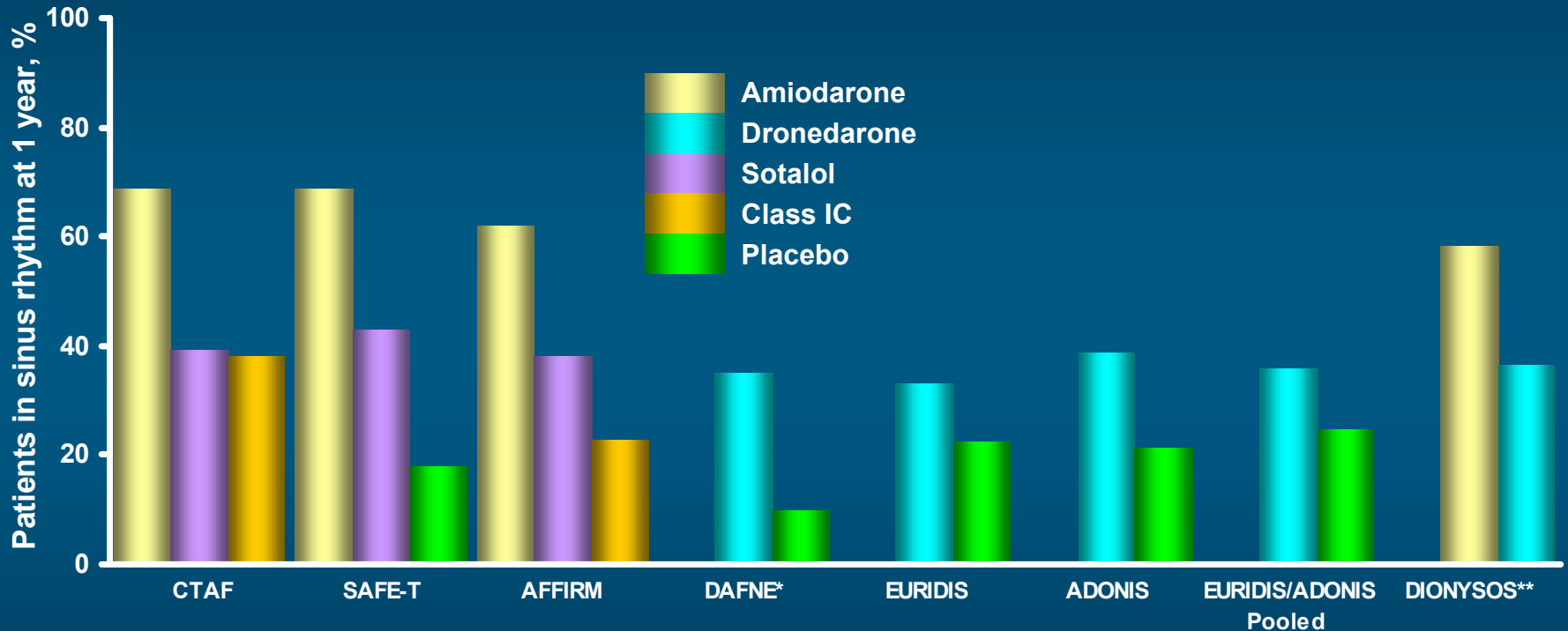
	Dronedarone	Amiodarone
AF recurrence or premature discontinuation	184	141
Recurrence of AF	158	107
Premature study drug discontinuation	26	34



Number at risk

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

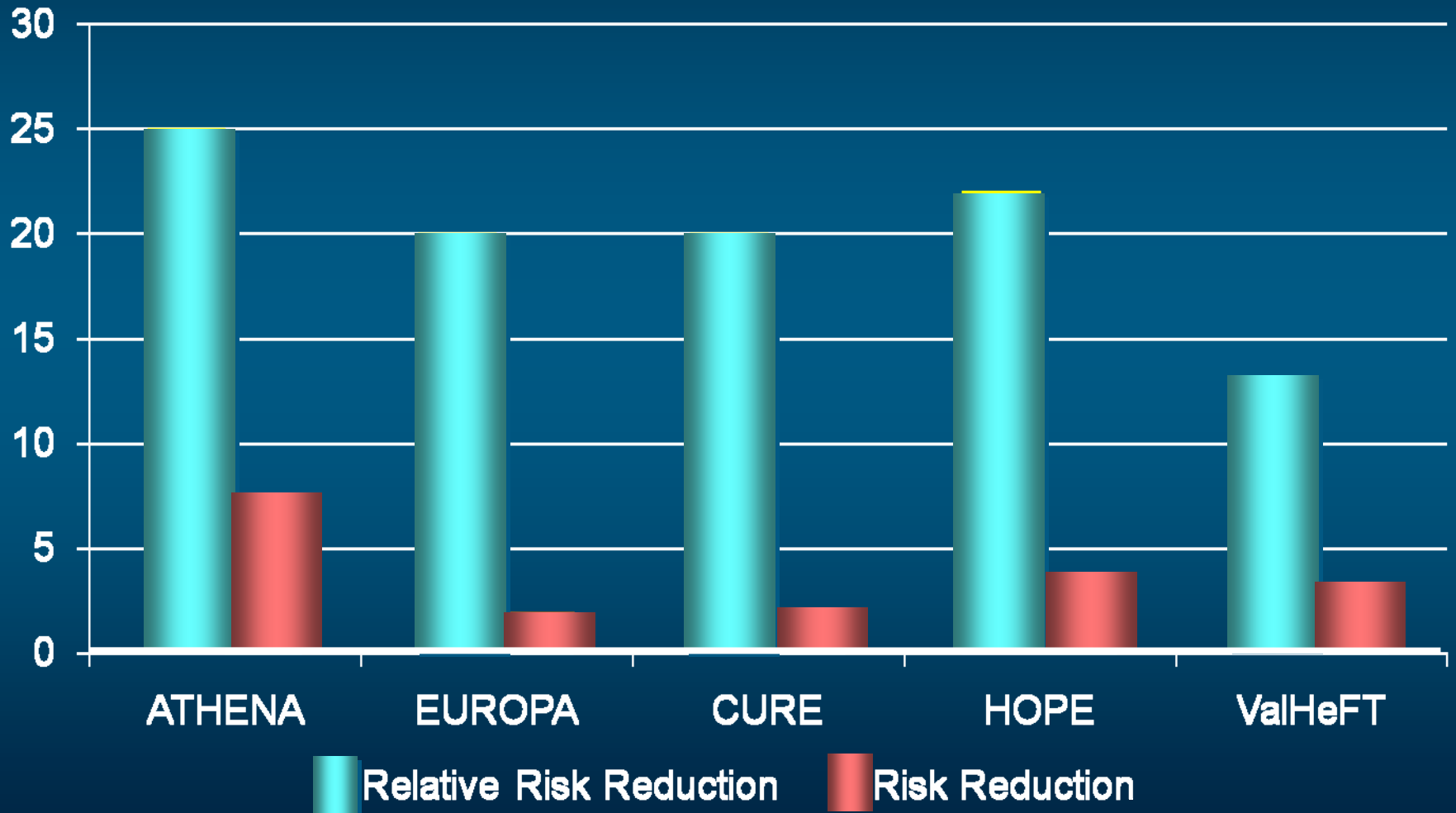
# Efficacy of Dronedarone and other AADs including Amiodarone in AF



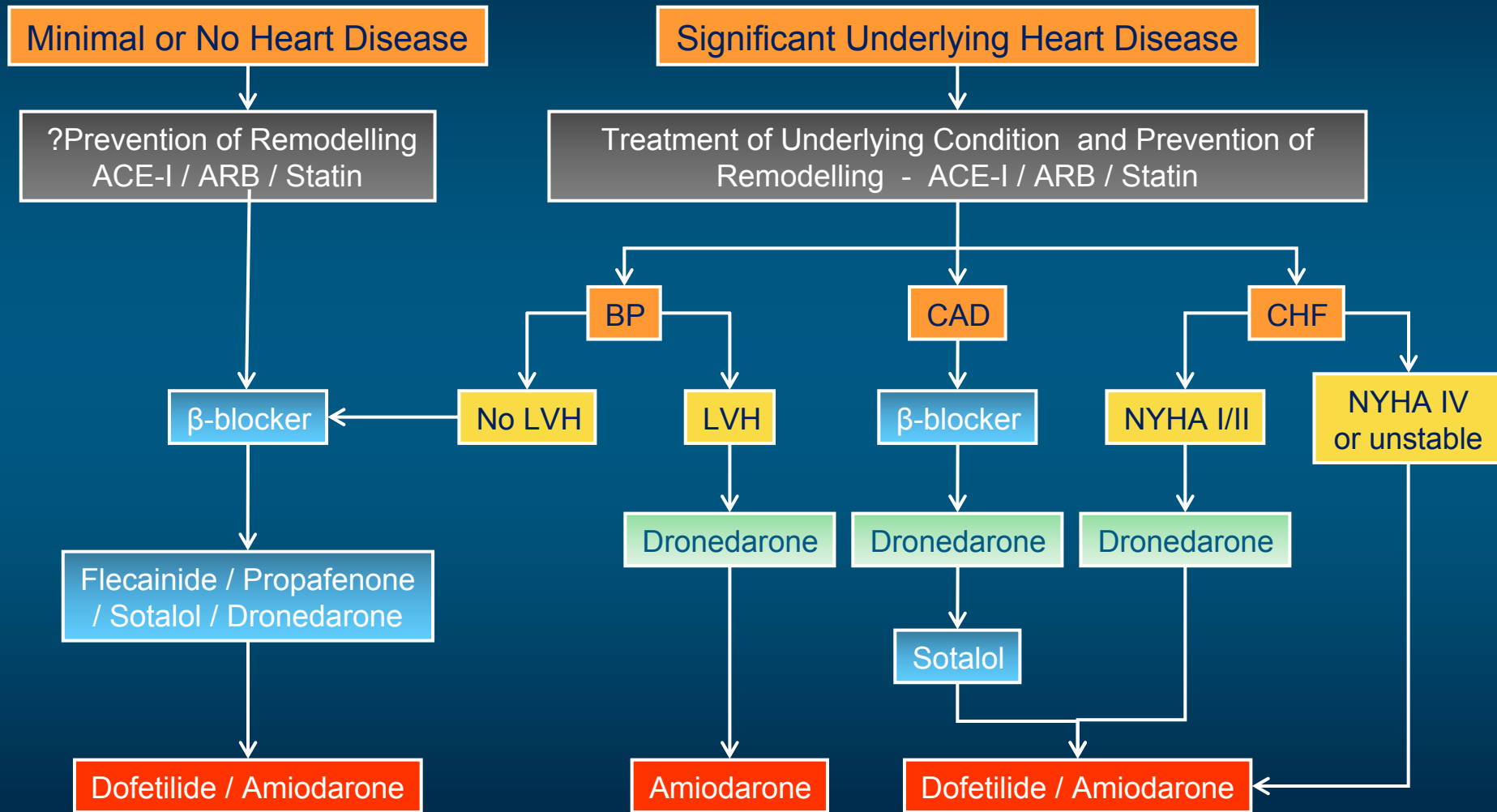
ADONIS = American-Australian-African trial with DronedarONE in atrial fibrillation or flutter for the maintenance of Sinus rhythm; AFFIRM = Atrial Fibrillation Follow up Investigation of Rhythm Management; CTAF = Canadian Trial of Atrial Fibrillation; DAFNE = Dronedarone Atrial Fibrillation study after Electrical cardioversion; DIONYSOS = Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation; EURIDIS = EUROpean trial in atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm; SAFE-T = Sotalol Amiodarone Atrial Fibrillation Efficacy Trial

\* At 6 months; \*\* mean follow-up 7 months

# Morbi-Mortality in CV Trials



# AAD “Guidelines” for AF Management



# Conclusions

- Thromboembolic prophylaxis will become simpler - better risk stratification - no monitoring - substantial take up - better results
- Rhythm control will again become an important clinical objective - better antiarrhythmic therapy – ablation and ?drugs
- Cardiovascular protection (in addition to rate and rhythm control) will become a major clinical objective, with upstream therapy, “antiarrhythmics” and ablation