

New Antiarrhythmics, what they do and who should initiate therapy?

Andrew Grace

Papworth Hospital and Cambridge University

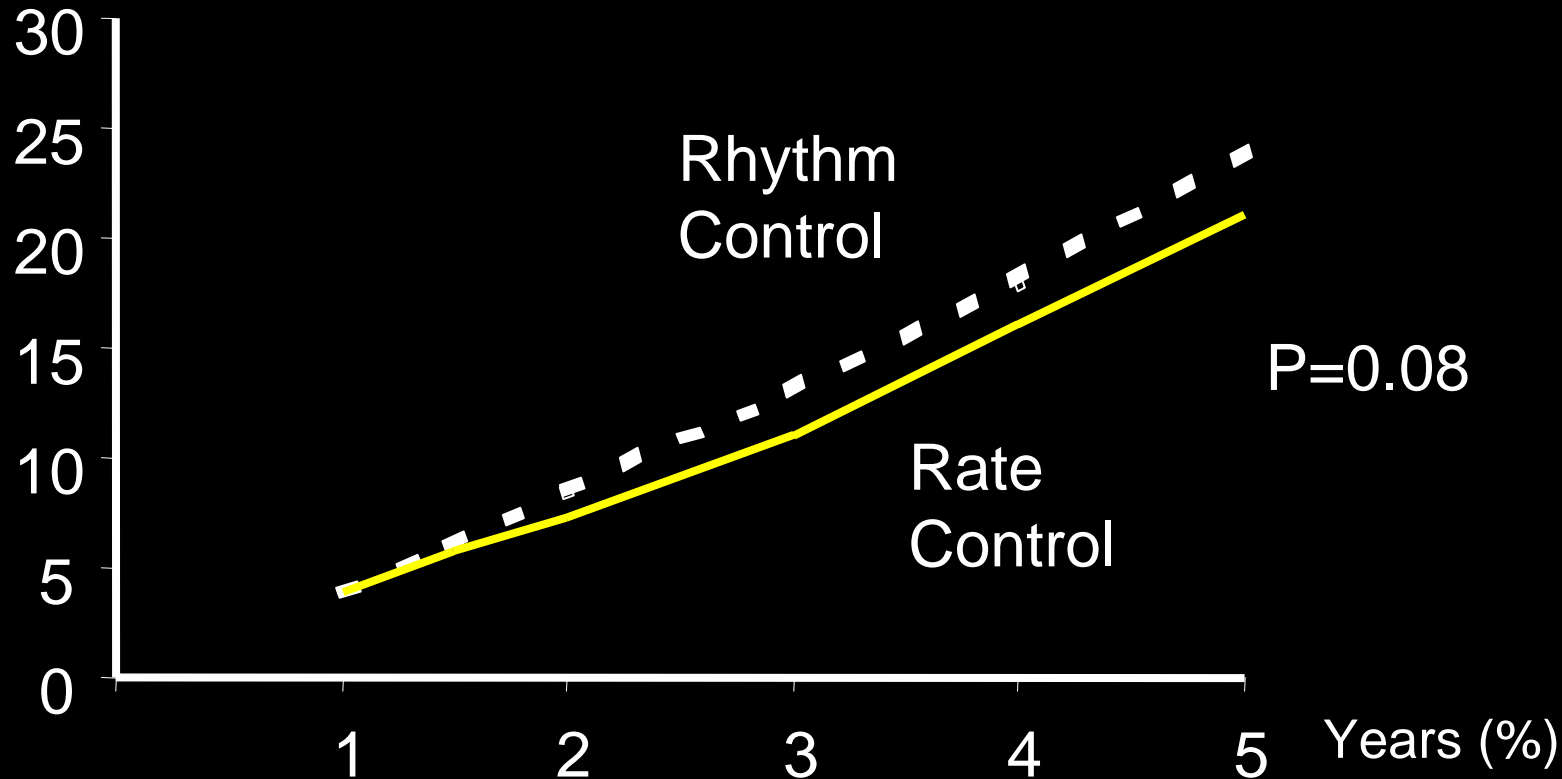
Conflicts of Interest: Consultant for Xention Ltd. and Sanofi-Aventis

Conventional Antiarrhythmic Drugs for AF

Rhythm Control vs. Rate Control (The AFFIRM Trial)

- N = 4060 patients, FU 5 years
- > 65 yr or other RF for Stroke or Death

Cumulative Mortality (%)



Impact of Atrial Fibrillation on Mortality

Mortality in AF Cases and Controls (Framingham Study)

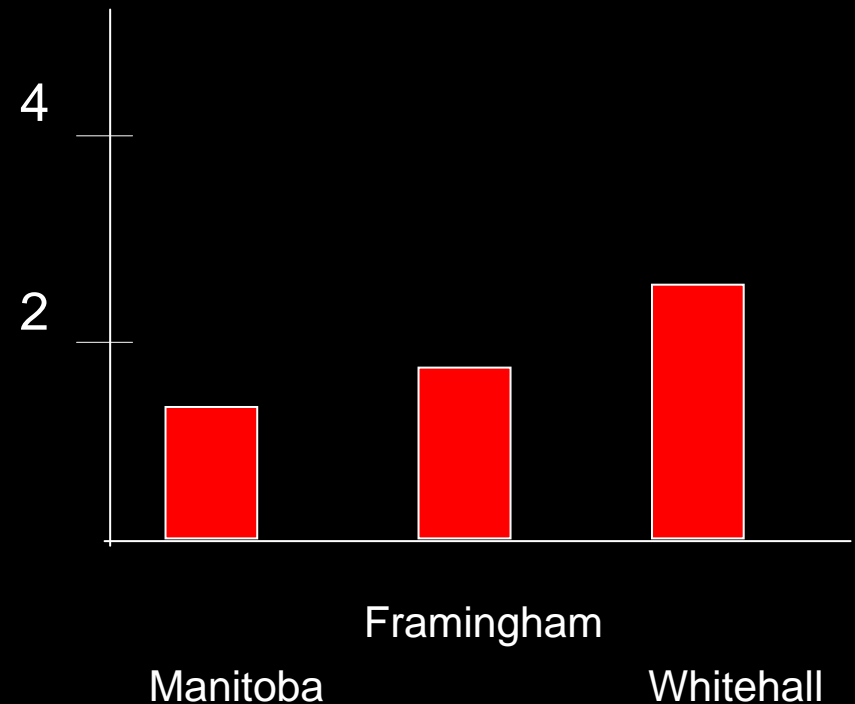
	AF (men)	Control (men)
Total deaths	59.2*	34.3
Deaths for CVS causes	49.9*	21.2
Average time to death	5.9yr*	7.7yr

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Relative Risk of Mortality



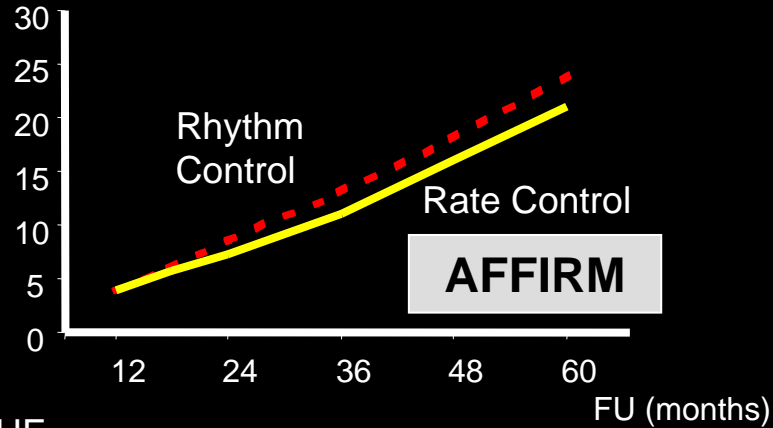
Kannel *et al.* NEJM 1982;306:1018

Fuster *et al.* Circulation 2006;108:1979

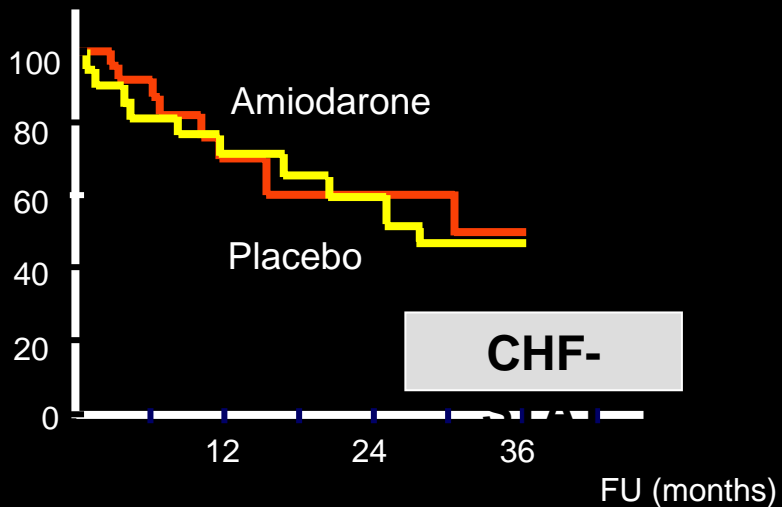
Importance of Sinus Rhythm

Rhythm vs Rate

Cumulative Mortality (%)

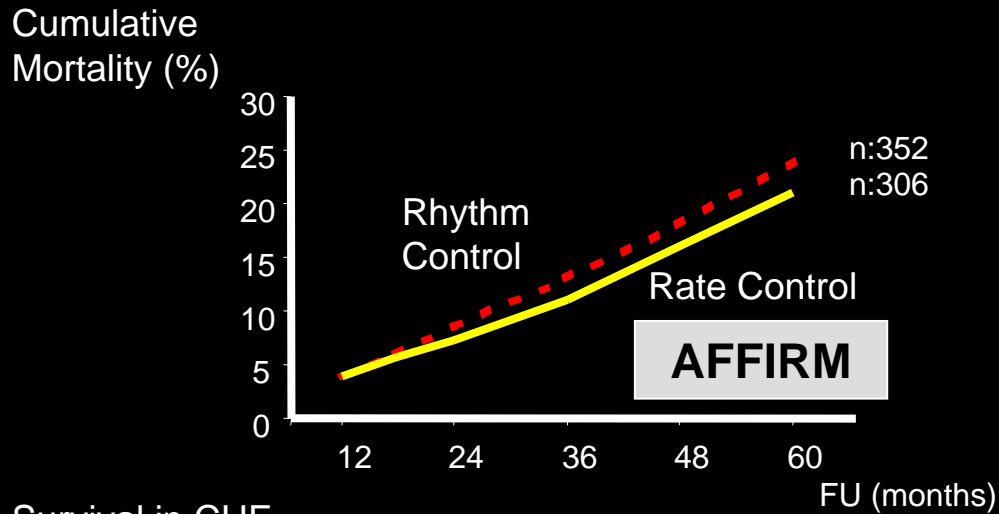


Survival in CHF and AF (%)

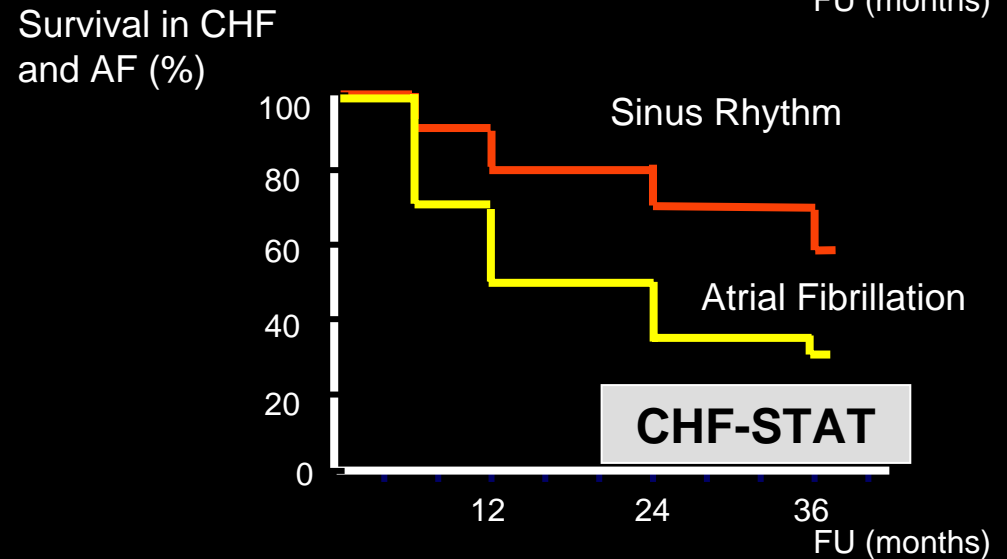
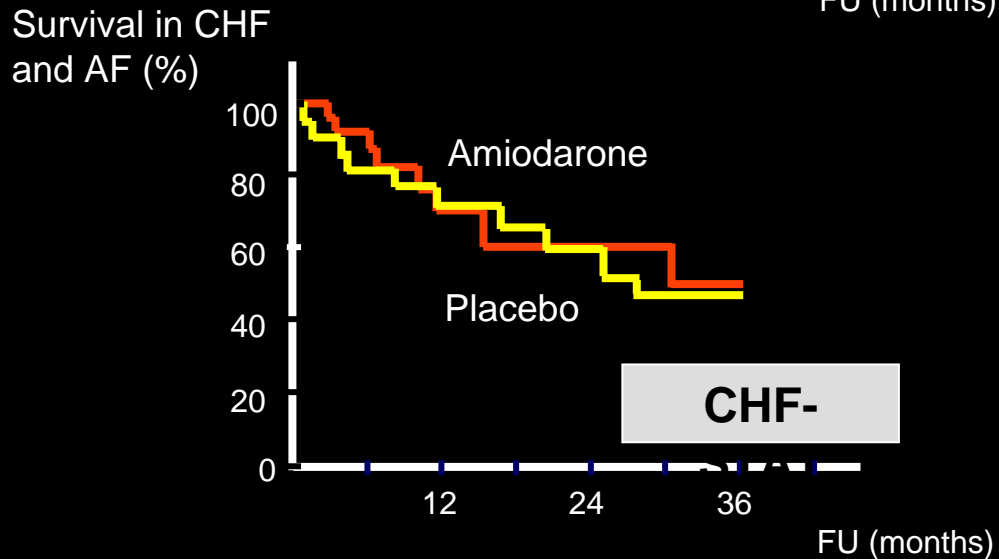
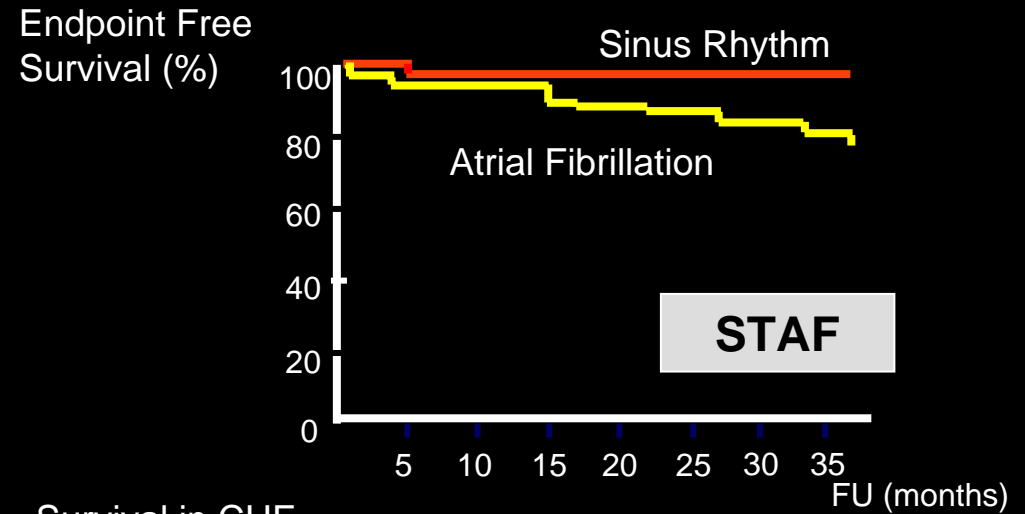


Importance of Sinus Rhythm

Rhythm vs Rate



Sinus vs AF



CAN SINUS RHYTHM IMPROVE SURVIVAL?

TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included

Covariate	P	HR	HR: 99% Confidence Limits	
			Lower	Upper
Age at enrollment*	<0.0001	1.06	1.05	1.08
Coronary artery disease	<0.0001	1.56	1.20	2.04
Congestive heart failure	<0.0001	1.57	1.18	2.09
Diabetes	<0.0001	1.56	1.17	2.07
Stroke or transient ischemic attack	<0.0001	1.70	1.24	2.33
Smoking	<0.0001	1.78	1.25	2.53
Left ventricular dysfunction	0.0065	1.36	1.02	1.81
Mitral regurgitation	0.0043	1.36	1.03	1.80
Sinus rhythm	<0.0001	0.53	0.39	0.72
Warfarin use	<0.0001	0.50	0.37	0.69
Digoxin use	0.0007	1.42	1.09	1.86
Rhythm-control drug use	0.0005	1.49	1.11	2.01

*Per year of age.

Predictors of Mortality in AFFIRM

A posteriori “on-treatment” analysis

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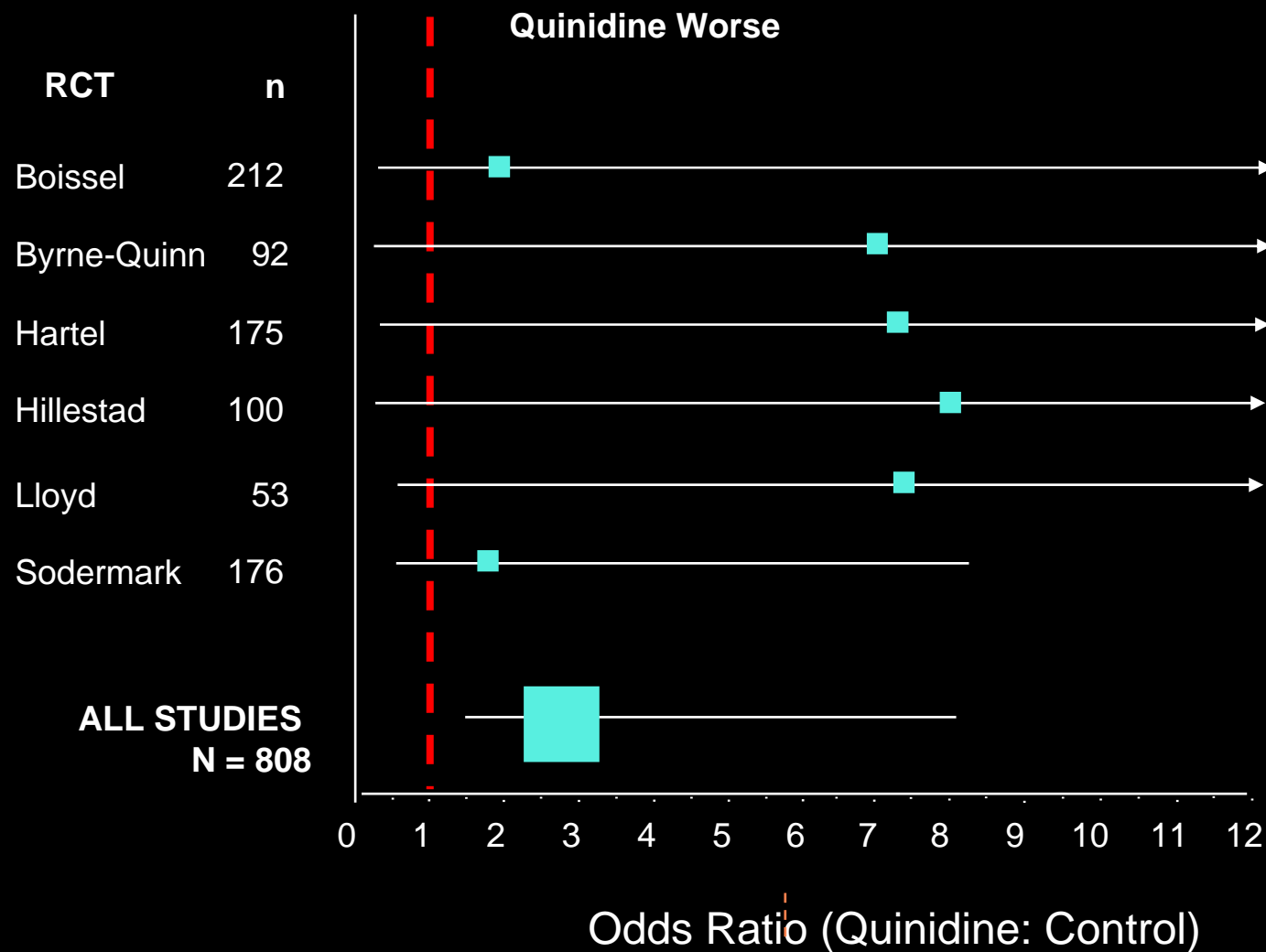
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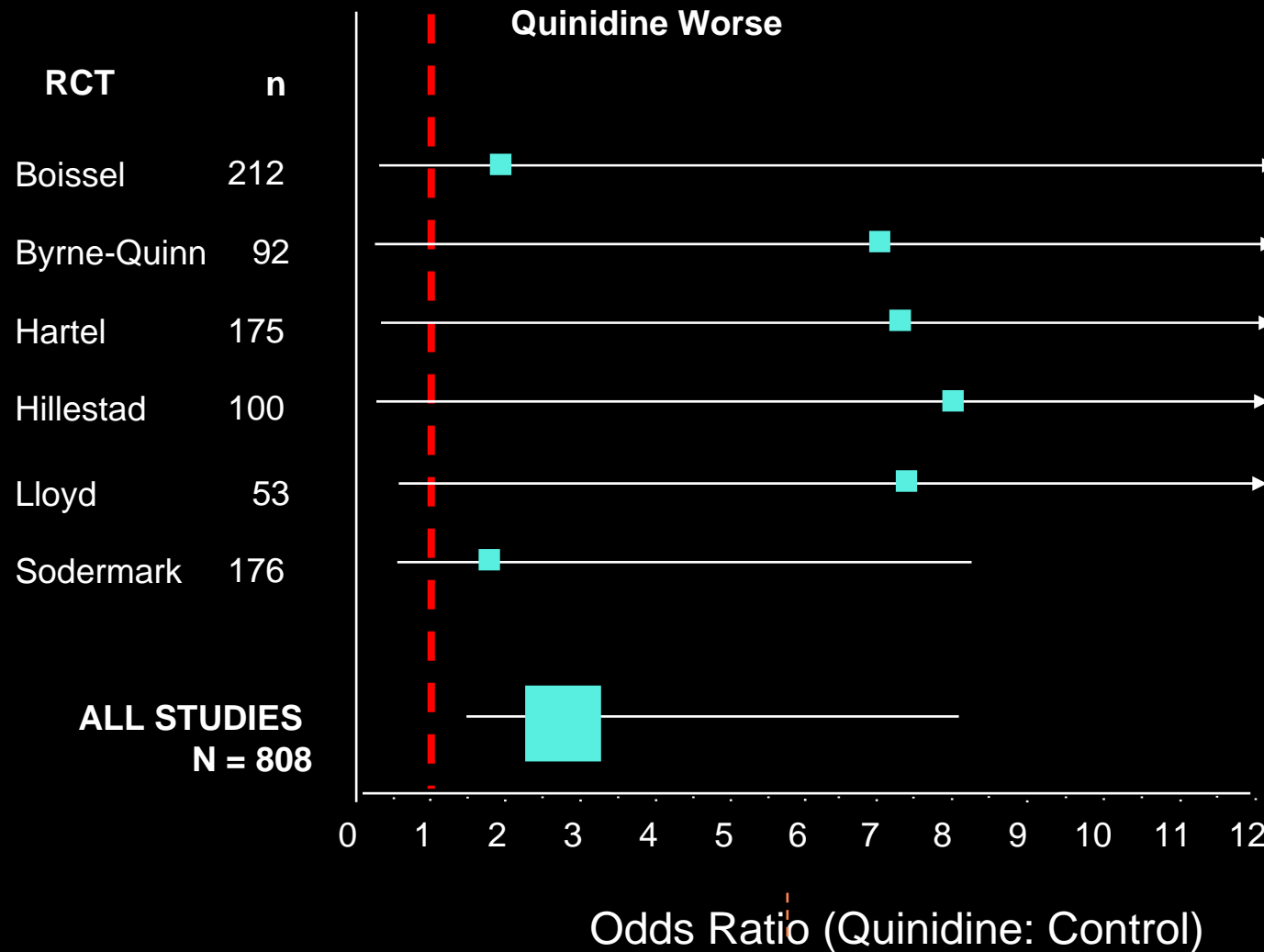
Predictors of Mortality in AFFIRM

A posteriori “on-treatment” analysis

Odds Ratio for Total Mortality for Patients Treated with Quinidine Compared to Control

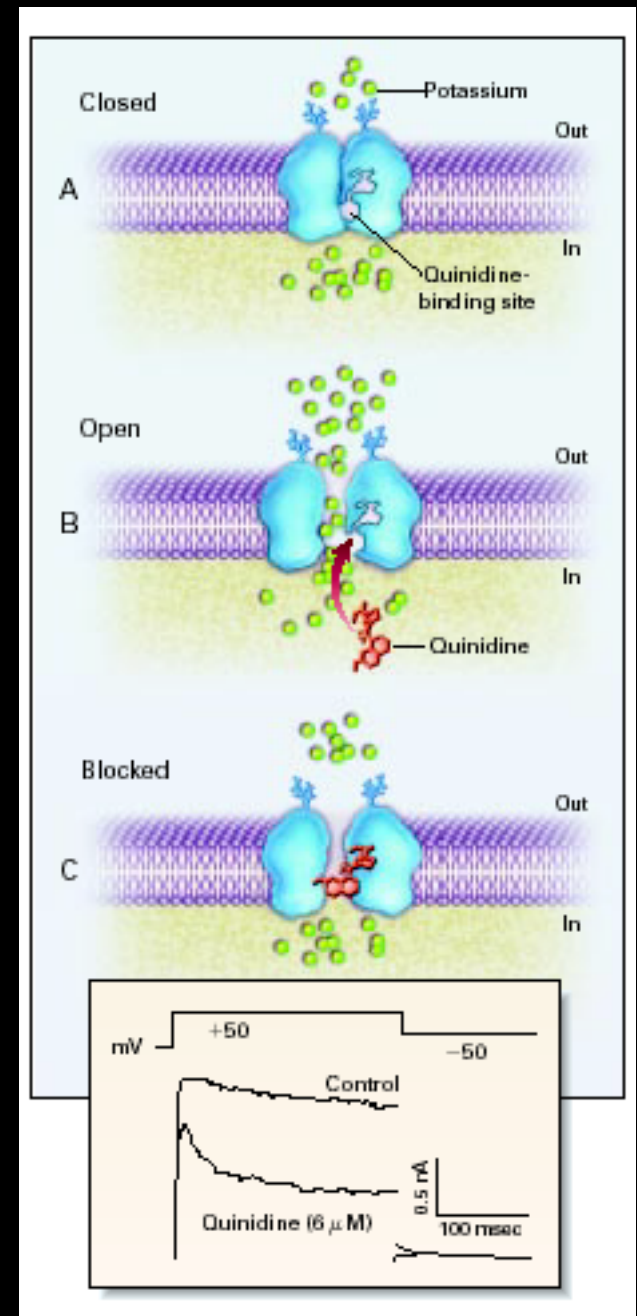


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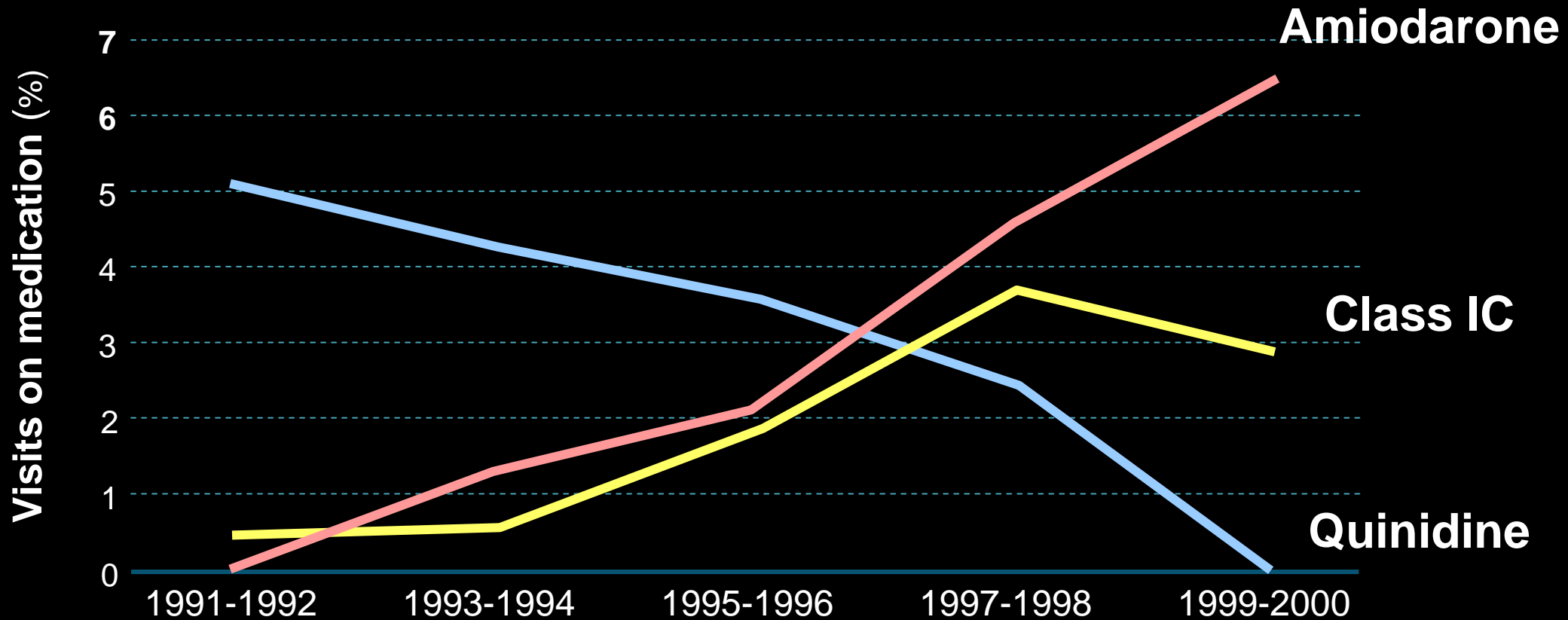


Coplen SE *et al.* *Circulation.* 1990;82:1106-1116.

Grace AA, Camm AJ *NEJM* 1998; 338:35-45

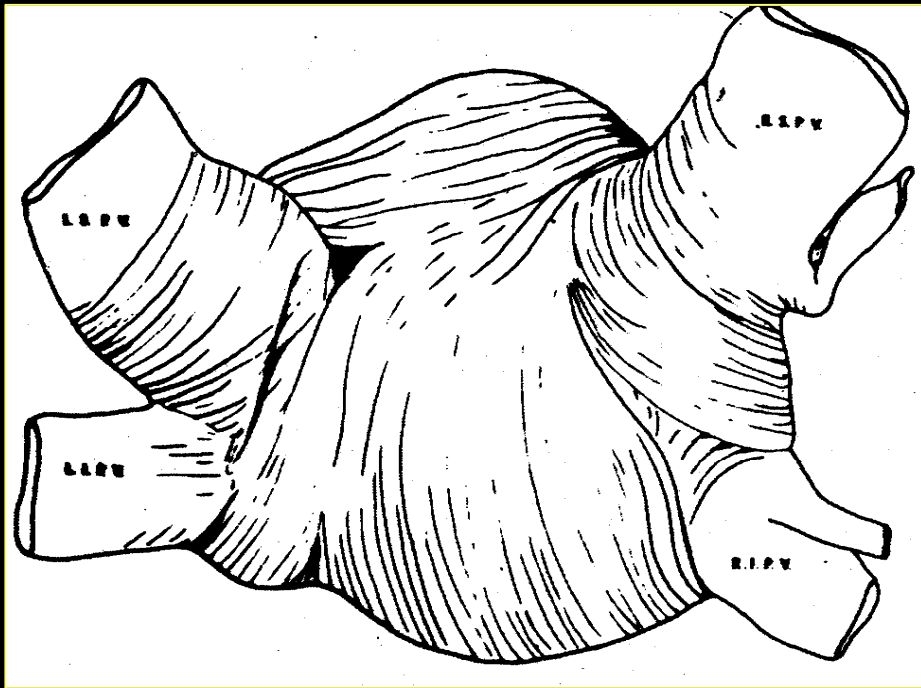


Physician Visits Associated with AAD Use 1990-2000



SUBSTRATE FOR ATRIAL FIBRILLATION

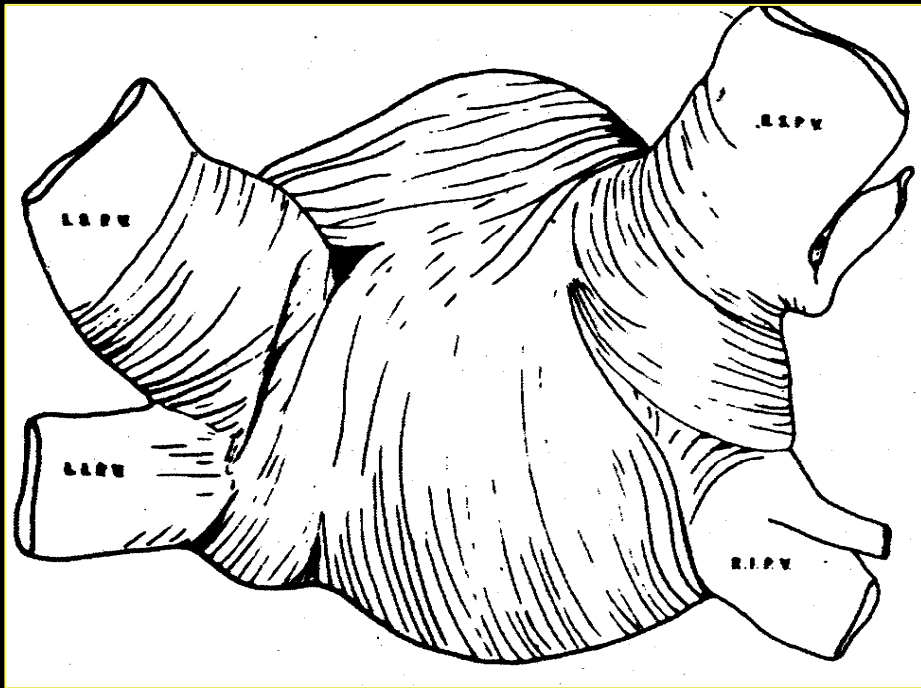
MUSCULATURE OF THE PULMONARY VEINS



Nathan and Eliakim Circulation 1966; 34:412

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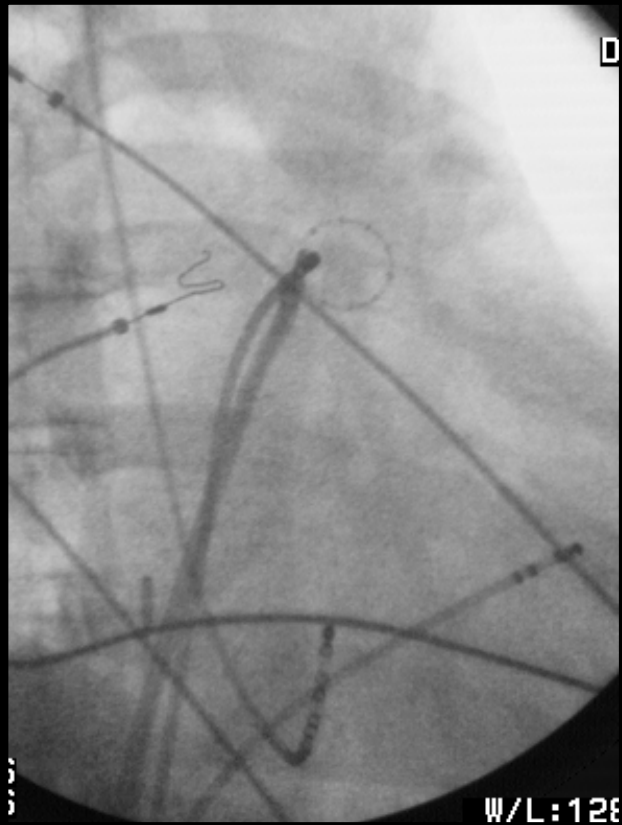


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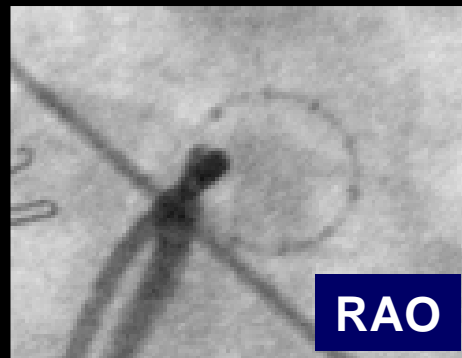
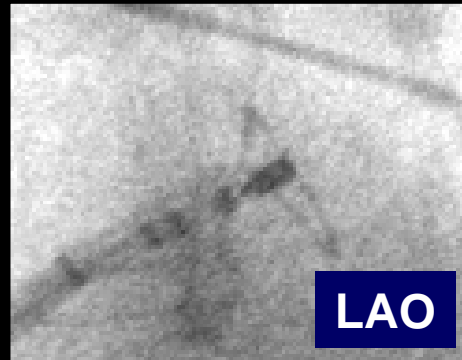
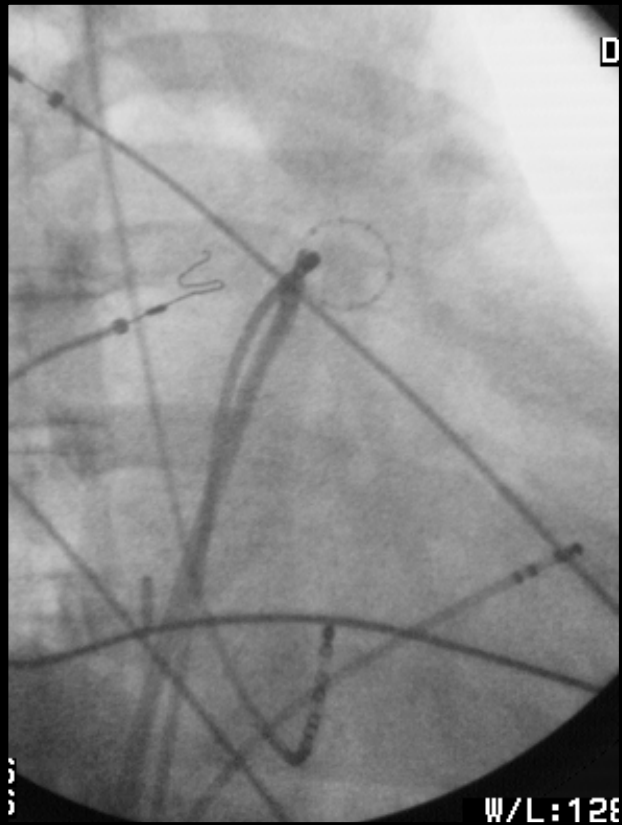


Haissaguerre *et al.* N Engl J Med 1998; 339:659

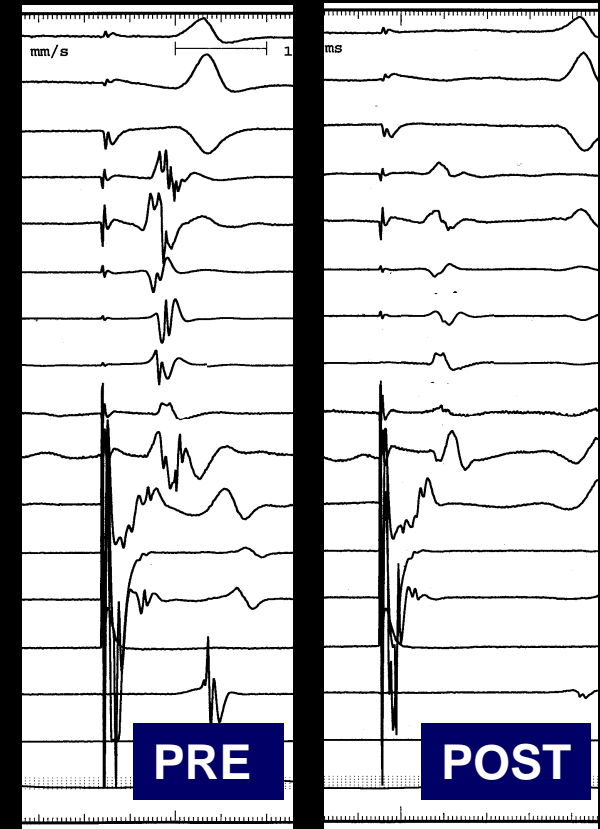
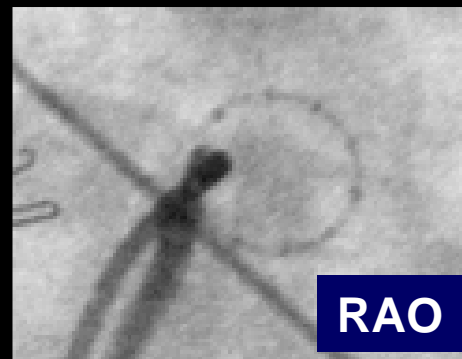
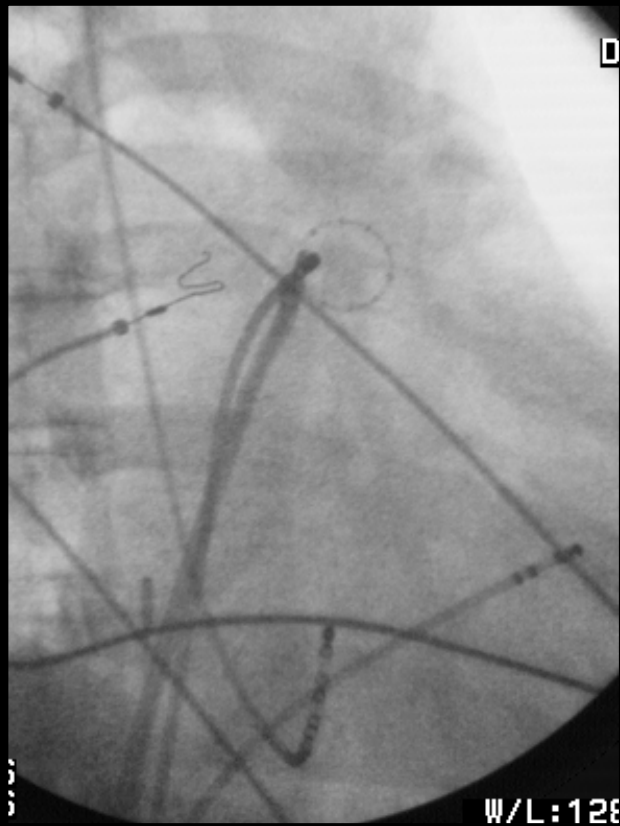
CIRCUMFERENTIAL OSTIAL MAPPING



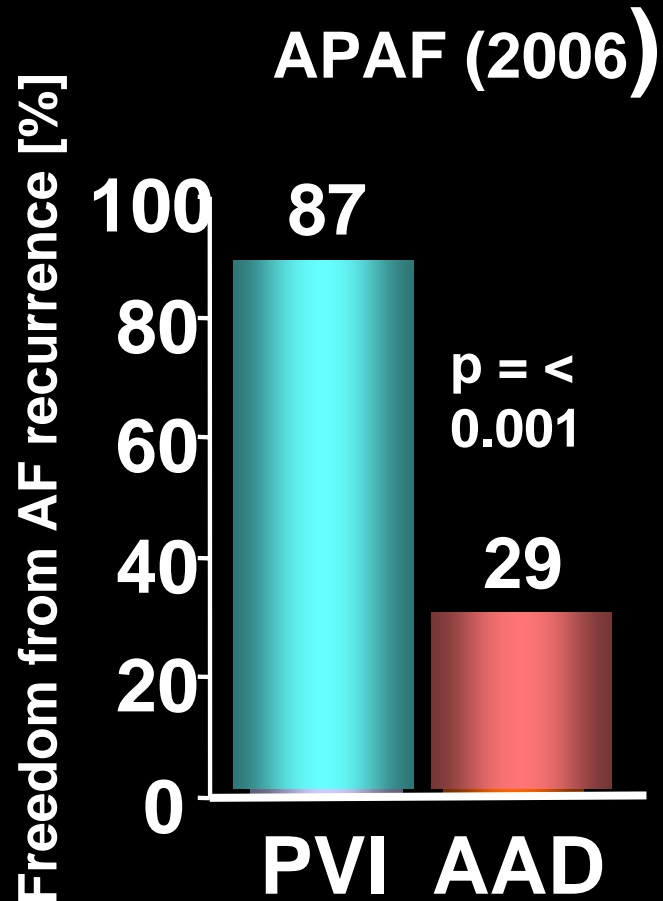
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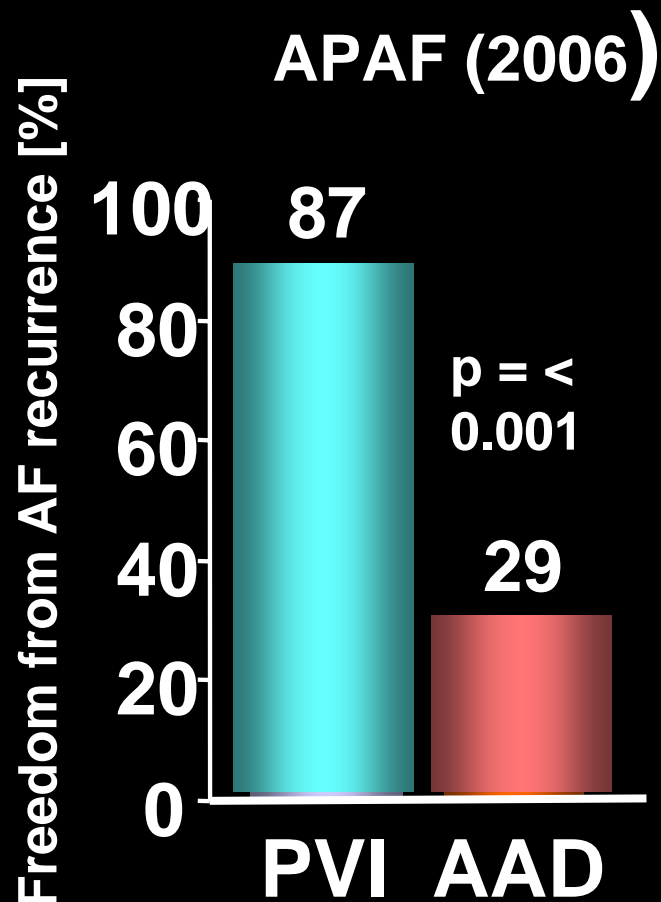
CIRCUMFERENTIAL OSTIAL MAPPING PULMONARY VEIN ISOLATION



AF Ablation vs. Antiarrhythmic Drugs?

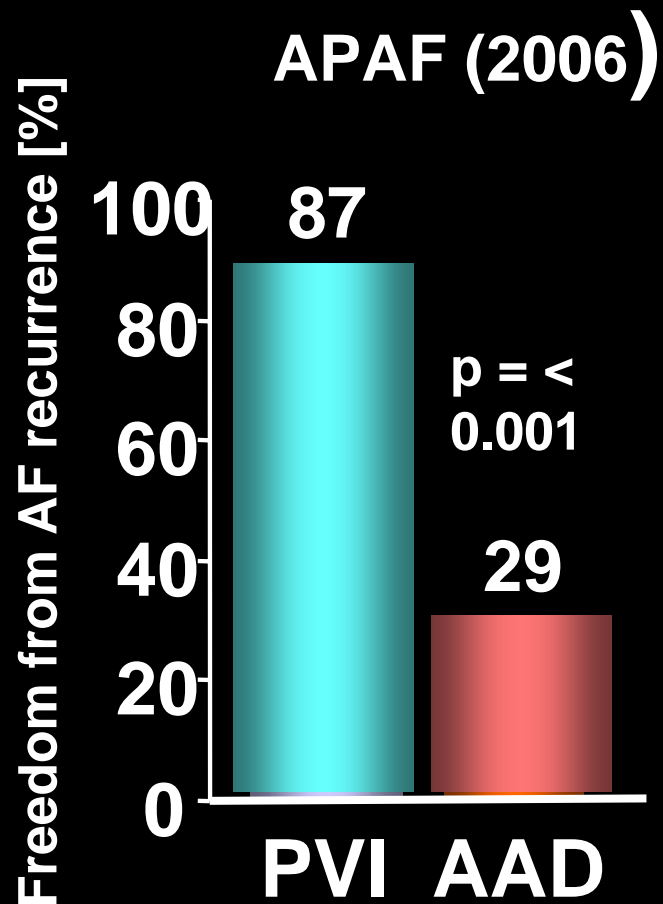


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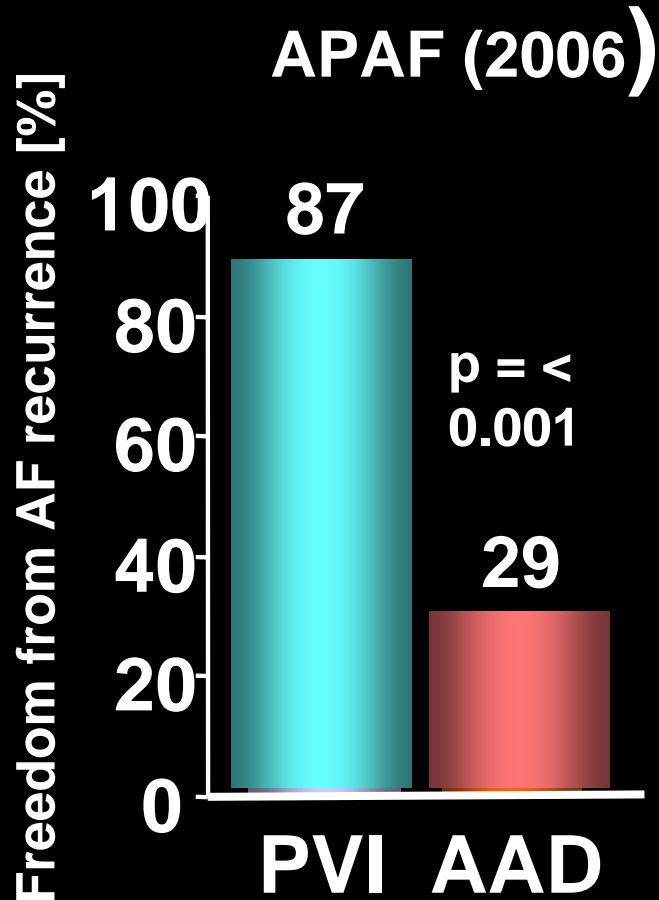
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		Ablation	AAD / control
Wazni et al, 2005 (RAAFT)	70	87%	37%
Stabile et al, 2005 (CACAF)	137	56%	9%
Oral et al, 2006	146	74%	4% (without amiodarone)
Pappone et al, 2006 (APAF)	189	87%	29%
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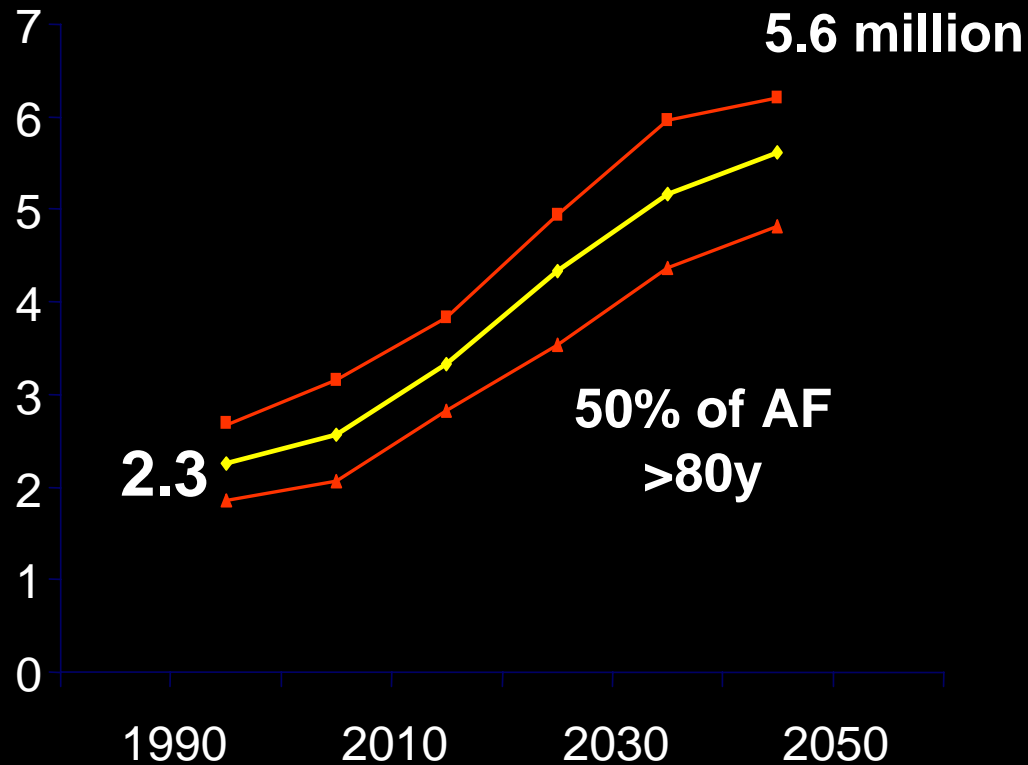


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Epidemiology of AF is Changing

Estimated Prevalence Pool at 2050

Projected N of Pts with AF (millions)



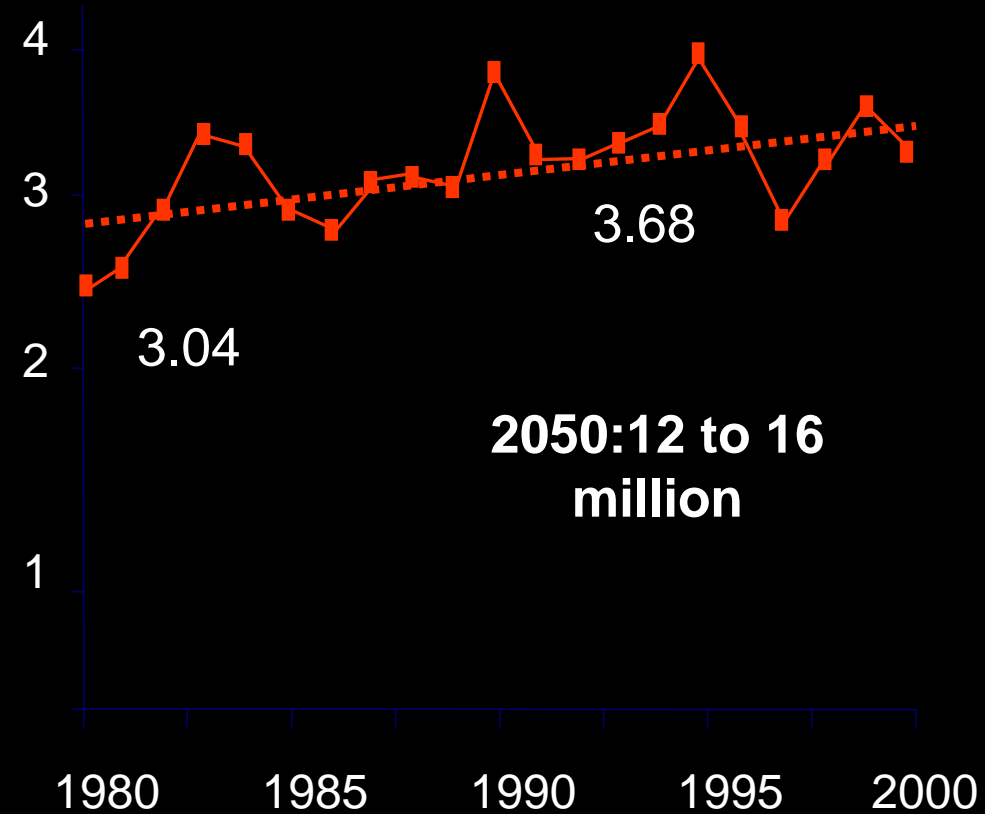
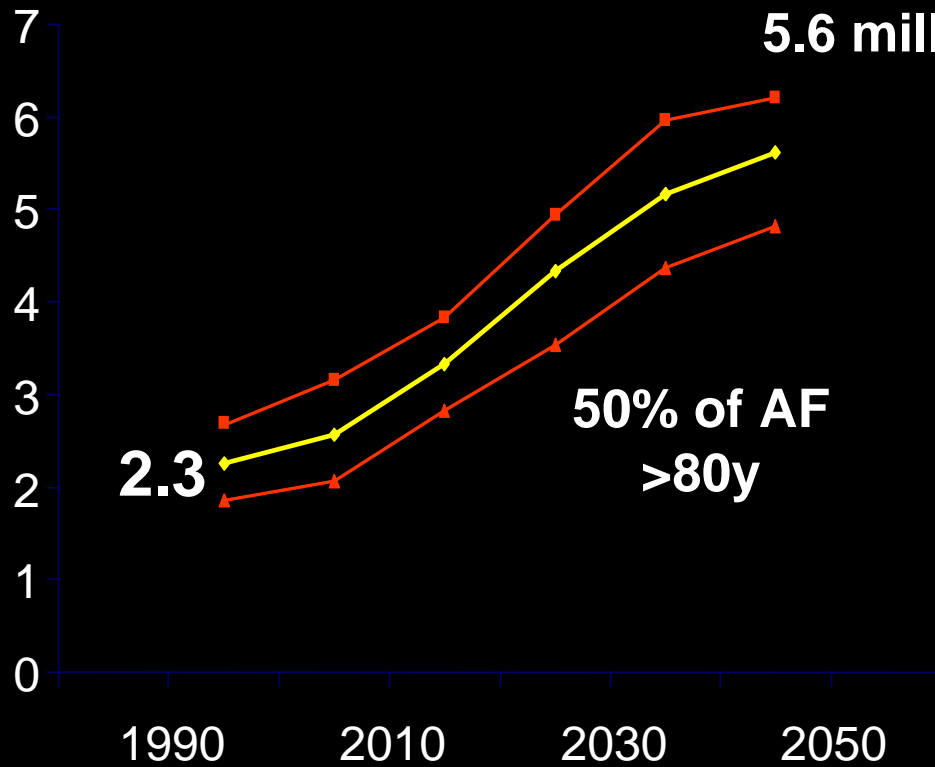
Go *et al*, JAMA 2001;285:2370

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Age-adjusted Incidence/1000 person-year

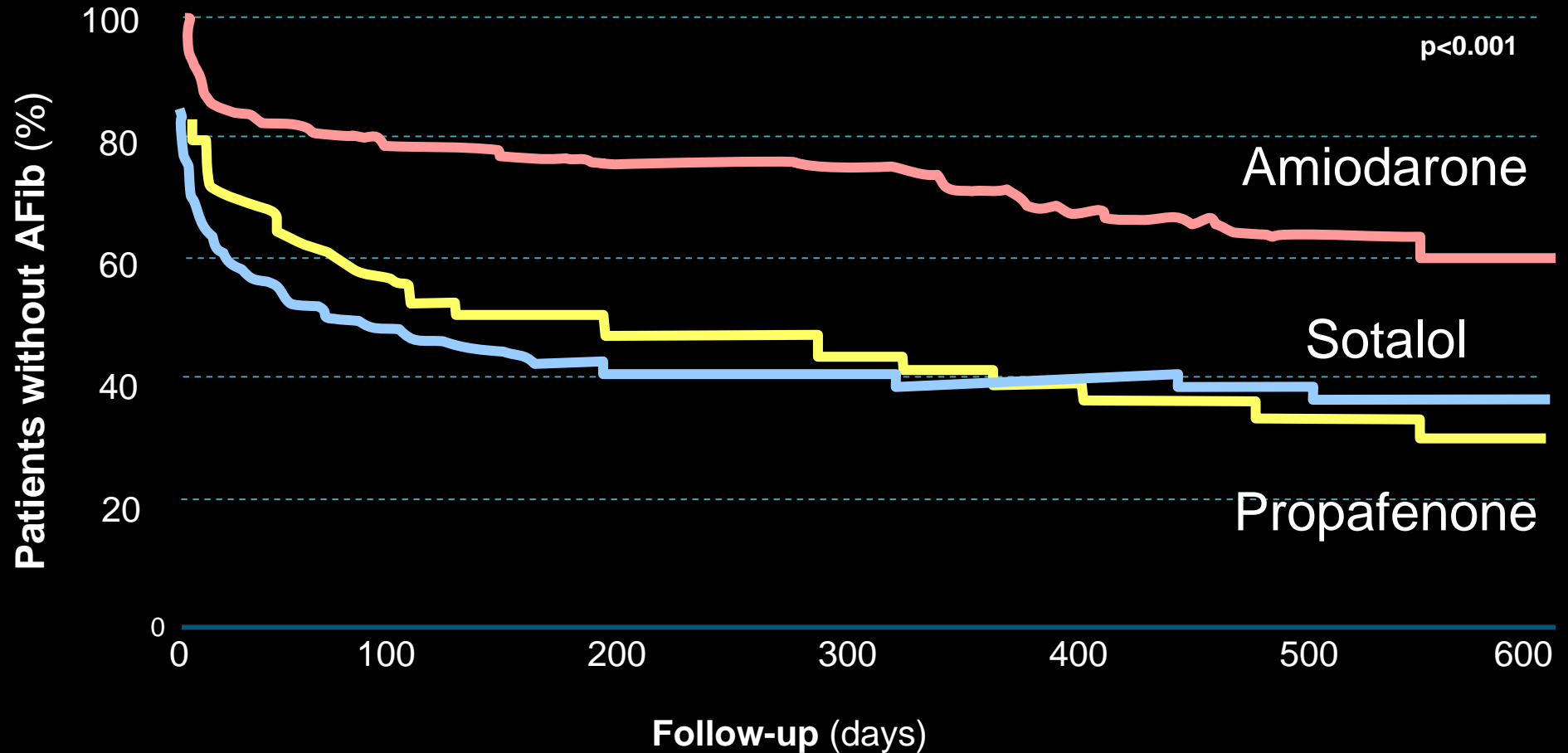


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Miyasaka *et al*, Circulation 2006;114:119

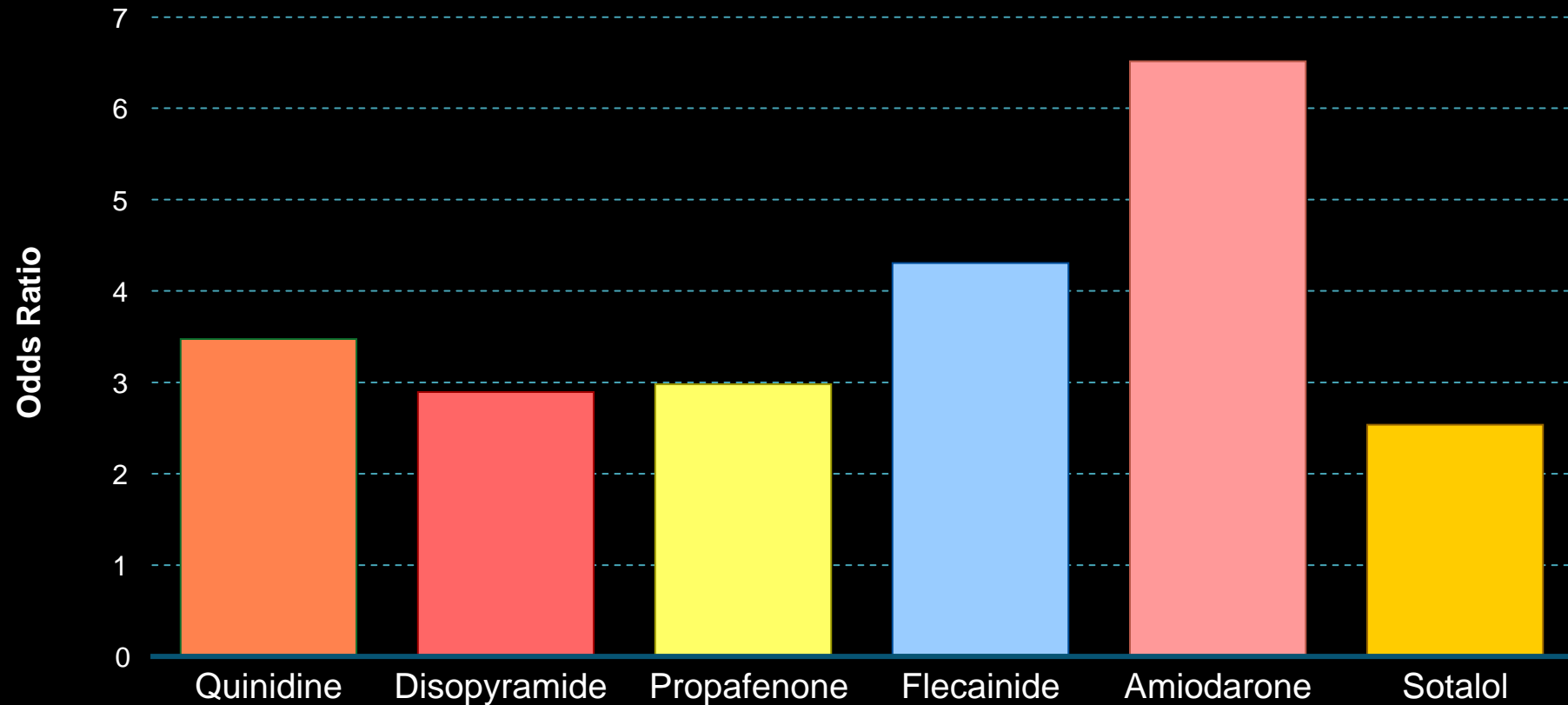
Amiodarone to Prevent Recurrence of AFib

CTAF Study: mean follow-up 16 months



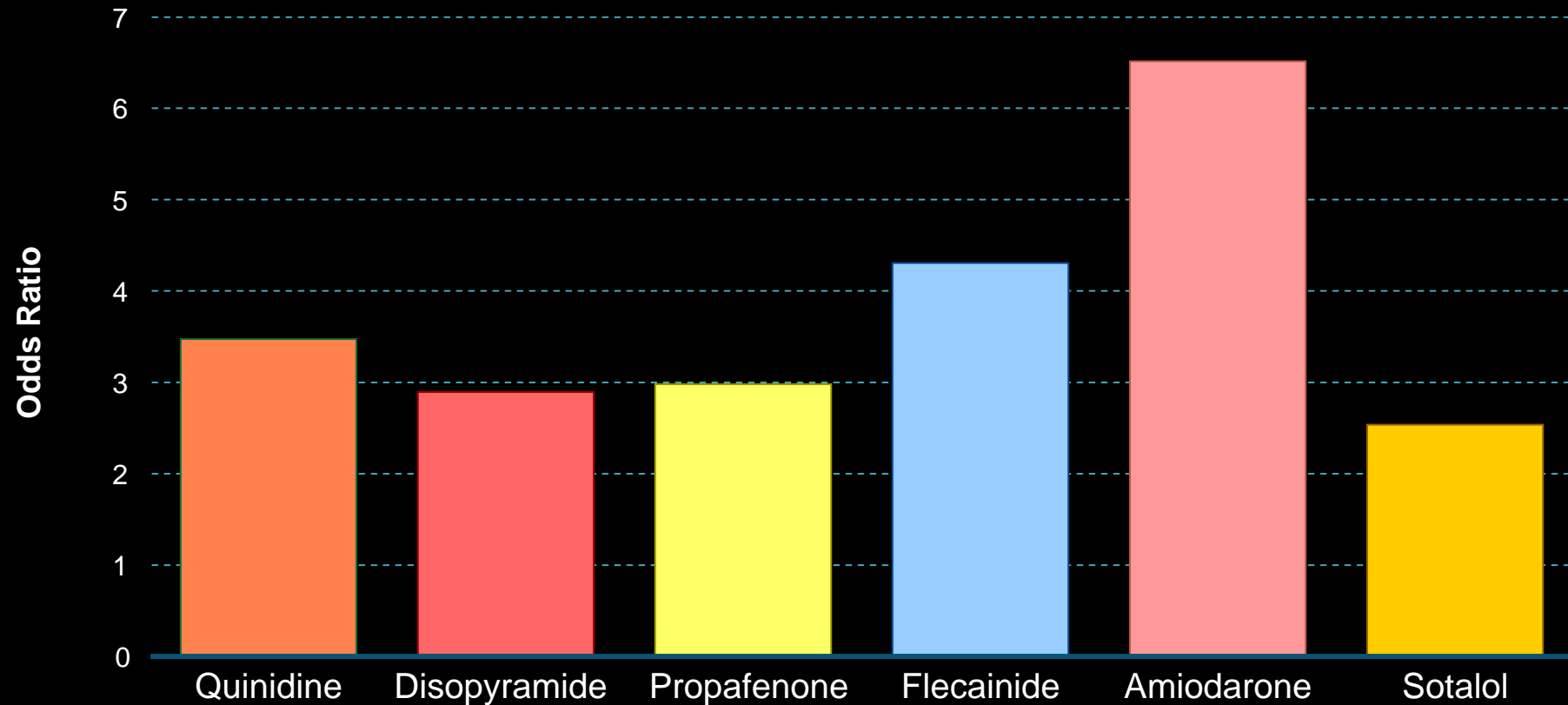
Antiarrhythmic Drugs for Maintenance of Sinus Rhythm

Meta-analysis of 18 randomized, controlled trials



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Amiodarone > risk of non-cardiac adverse effects

Amiodarone is a difficult drug



Major Adverse Experiences Associated with Early Amiodarone Discontinuation

- Hypothyroidism **7.0%**
- Hyperthyroidism **1.4%**
- Peripheral Neuropathy **0.5%**
- Lung Infiltrates **1.6%**
- Liver Dysfunction **1.0%**
- Bradycardia **2.4%**

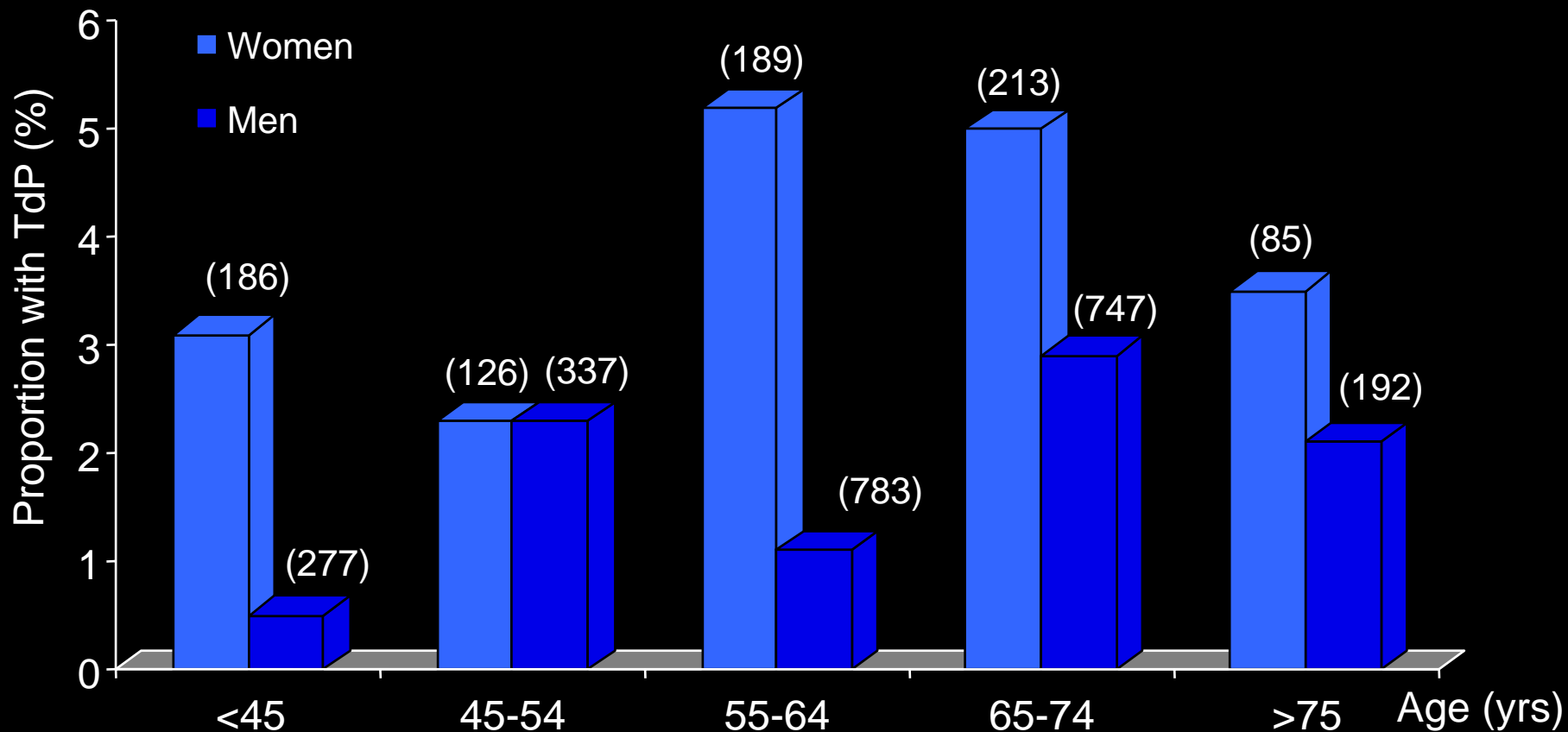
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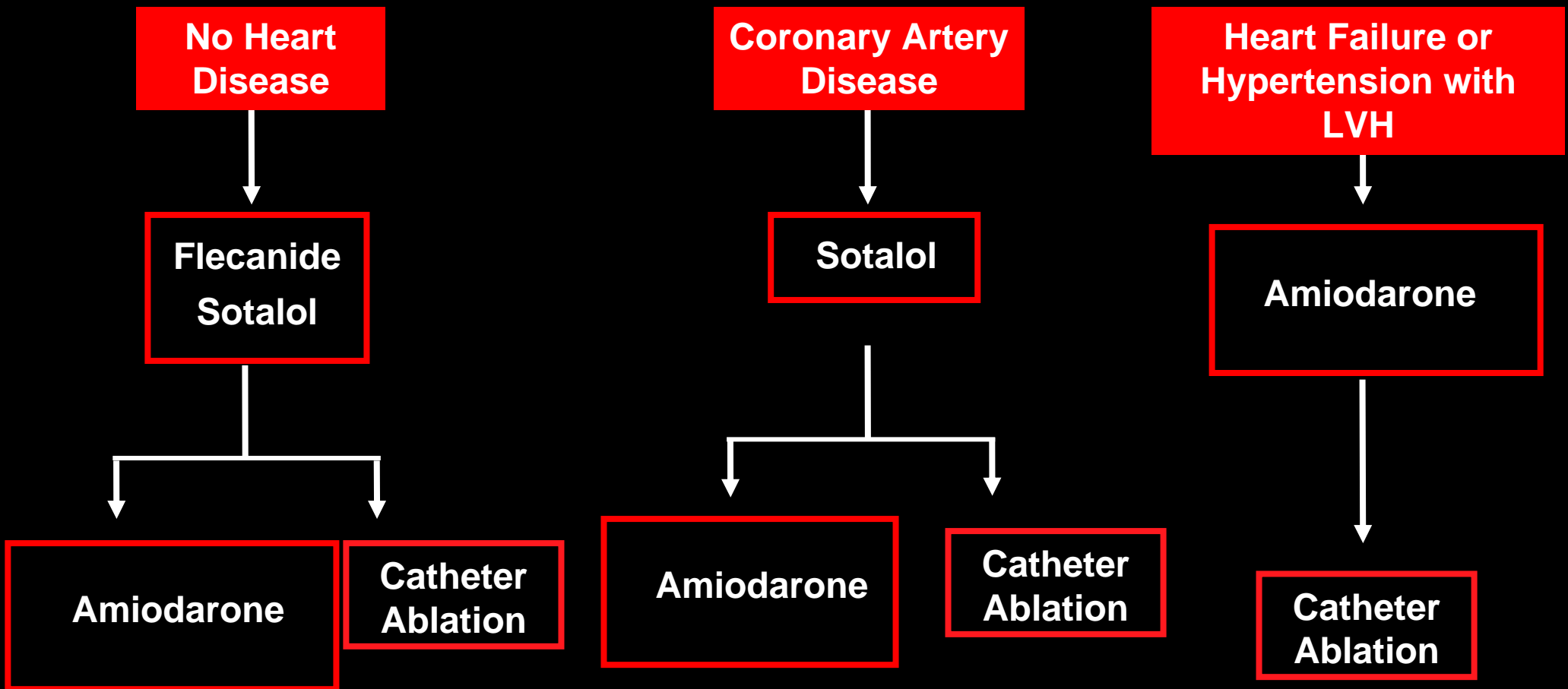
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Torsade de Pointes and d,l-Sotalol



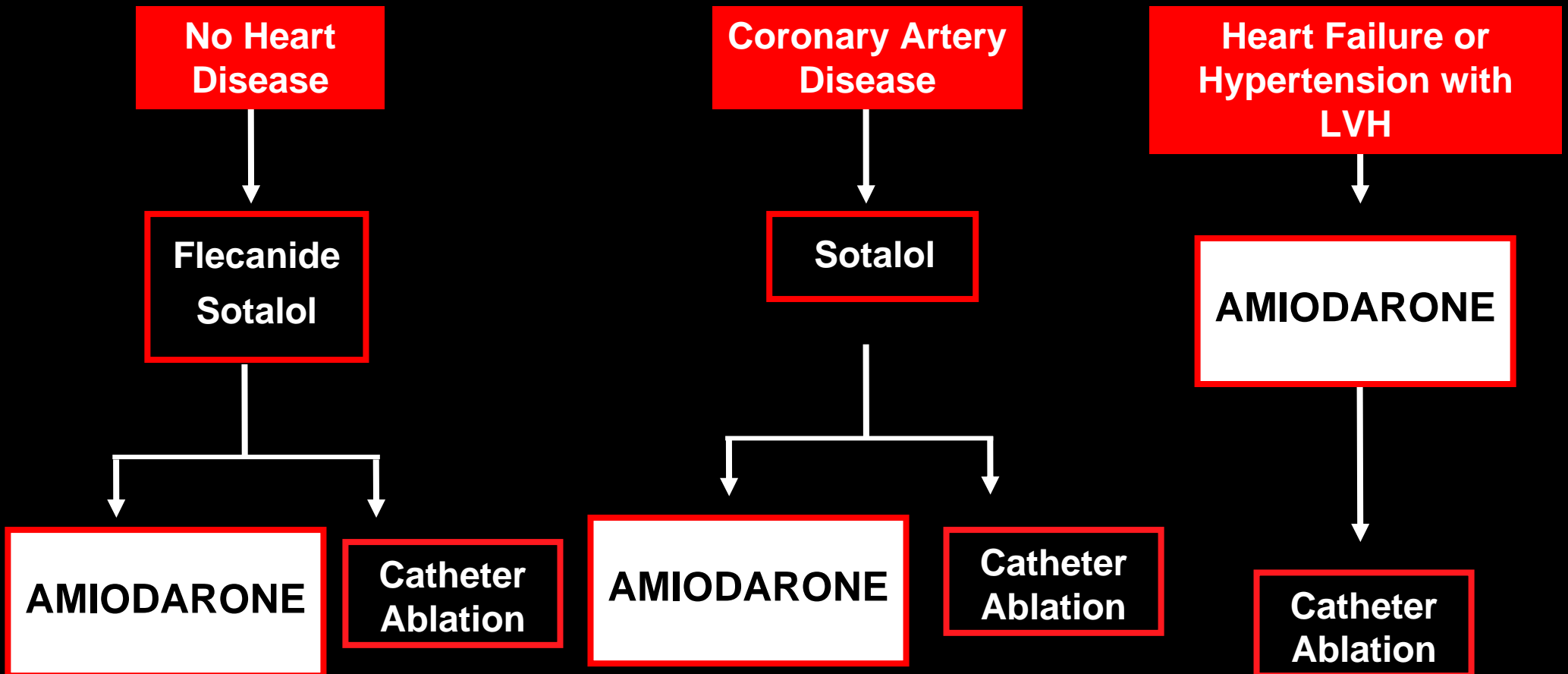
Conventional Antiarrhythmic Drugs for AF

ACC/AHA/ESC 2006 guidelines for the management of AF



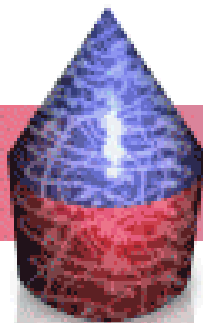
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Better Drugs: Re-engineering

(ARYx Retrometabolic Engineering (ARM))



Identify Target Molecule

- Large, chronic, oral market
- Do problems exist that we can fix?
 - CYP450 clearance
 - Drug-drug interactions
 - Off-target problems



Design "Ideal" Metabolite

- Inactive
- Non-toxic
- Rapidly eliminated by non-CYP450 pathway
- Water soluble

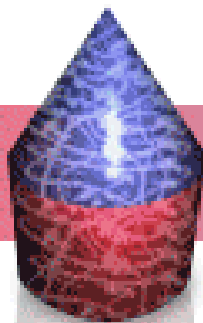


Create ARYx Product

- Retains desired efficacy
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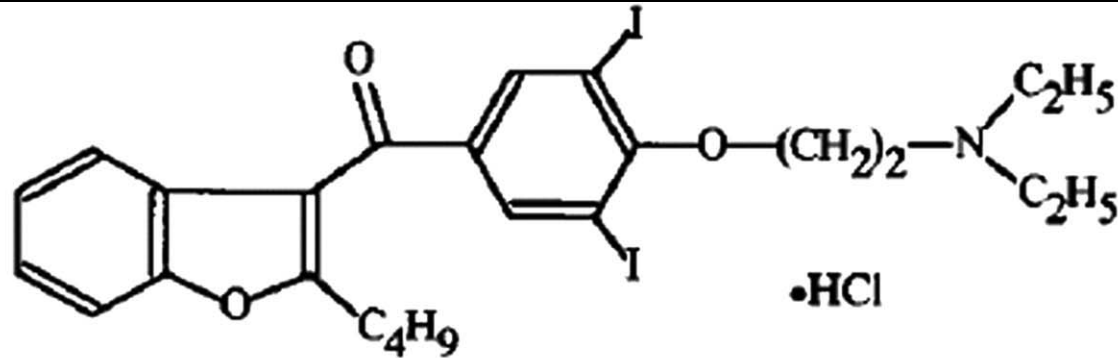


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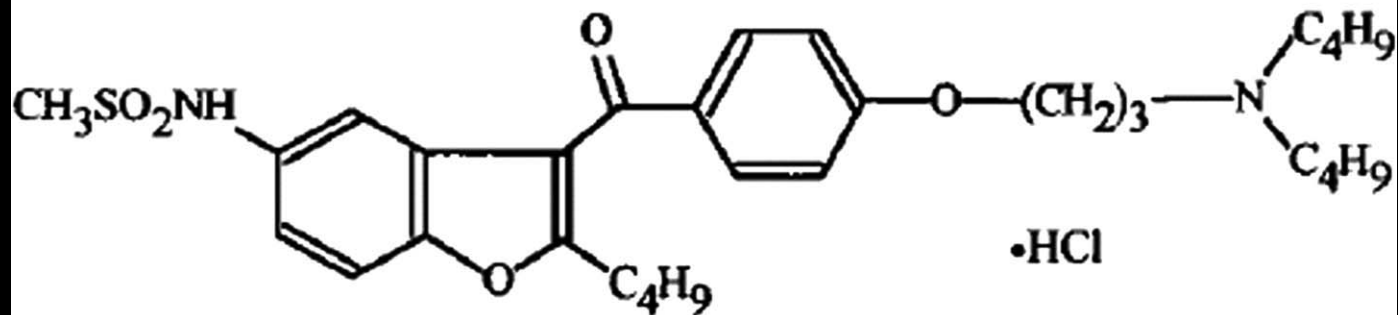
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- **Budiodarone (ATI-2042) – chemical analogue amiodarone ‘intentionally’ contains iodine**
- **Completed pilot phase II PASCAL (PAF with continuous AF logging) – HRS, May 2009**

Amiodarone and Dronedarone

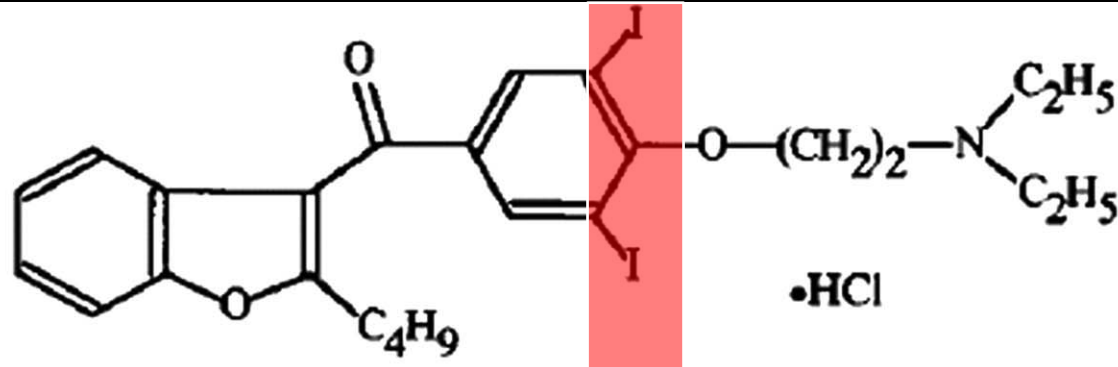


Amiodarone (MW=682)

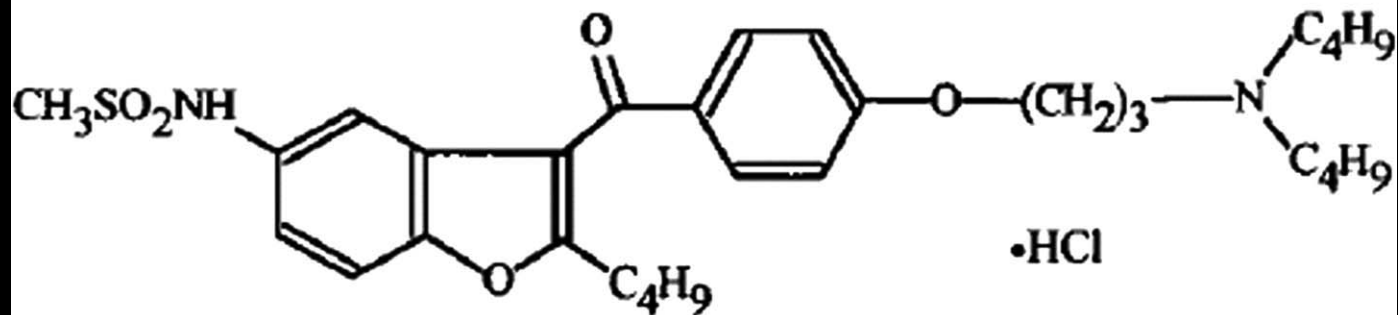


SR33589B/Dronedarone (MW=593)

Amiodarone and Dronedarone



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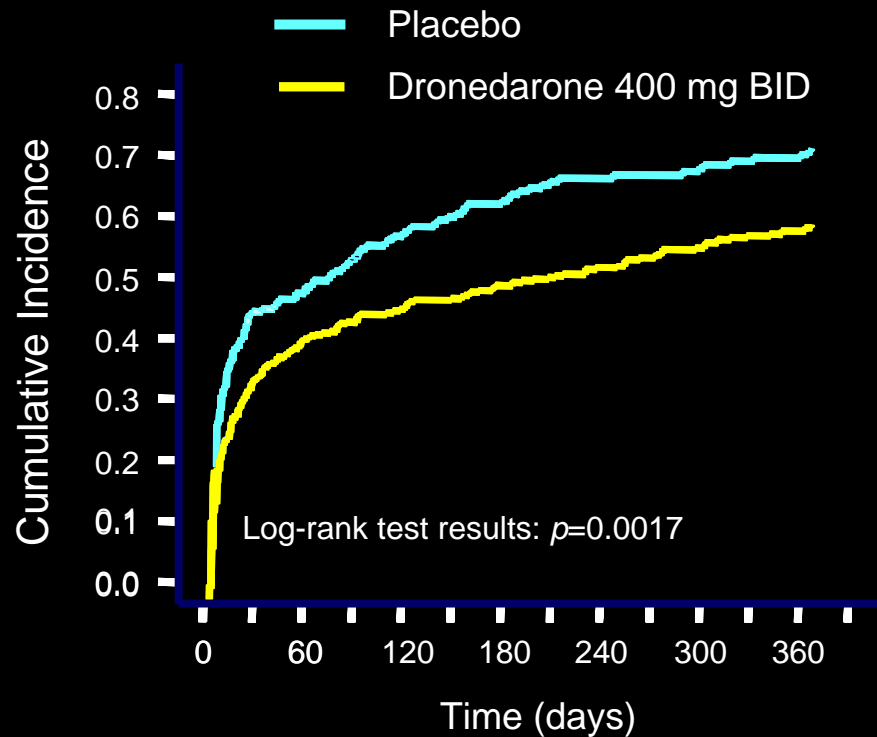


SR33589B/Dronedarone (MW=593)

Dronedarone (Post-Hoc Analysis)

ADONIS (N=630, follow-up 1 year)

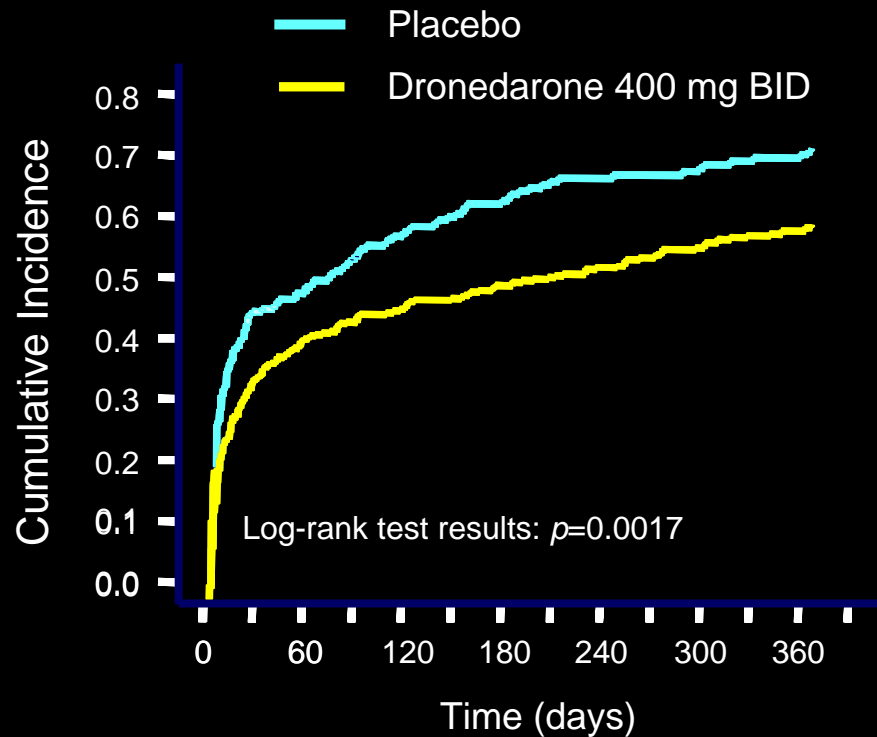
Time to AF Recurrence



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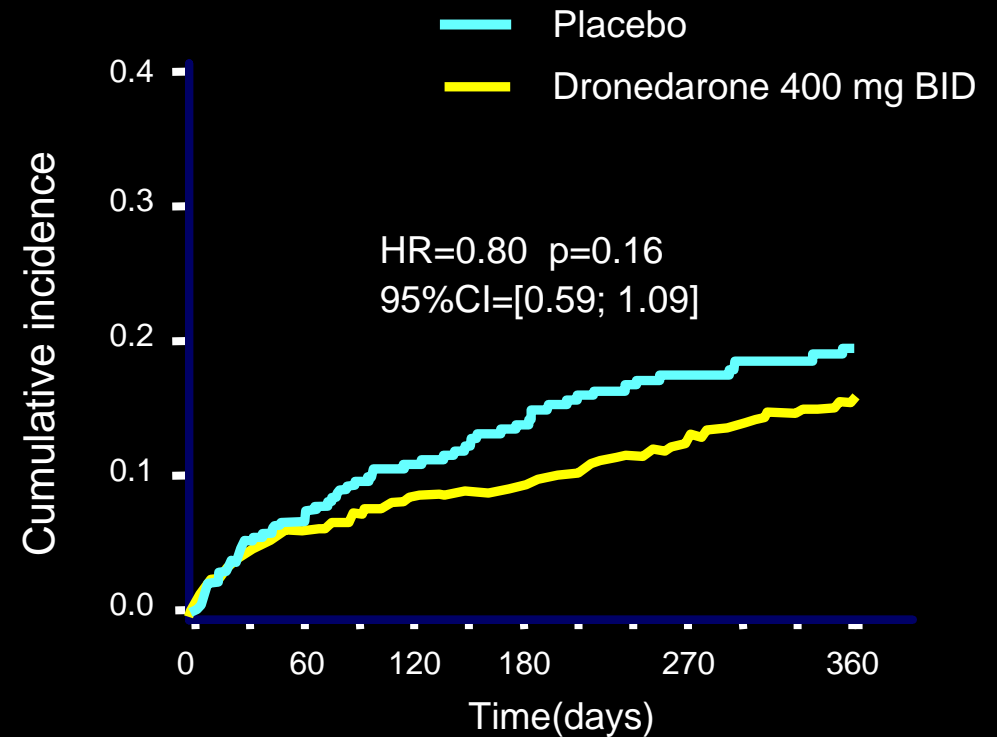
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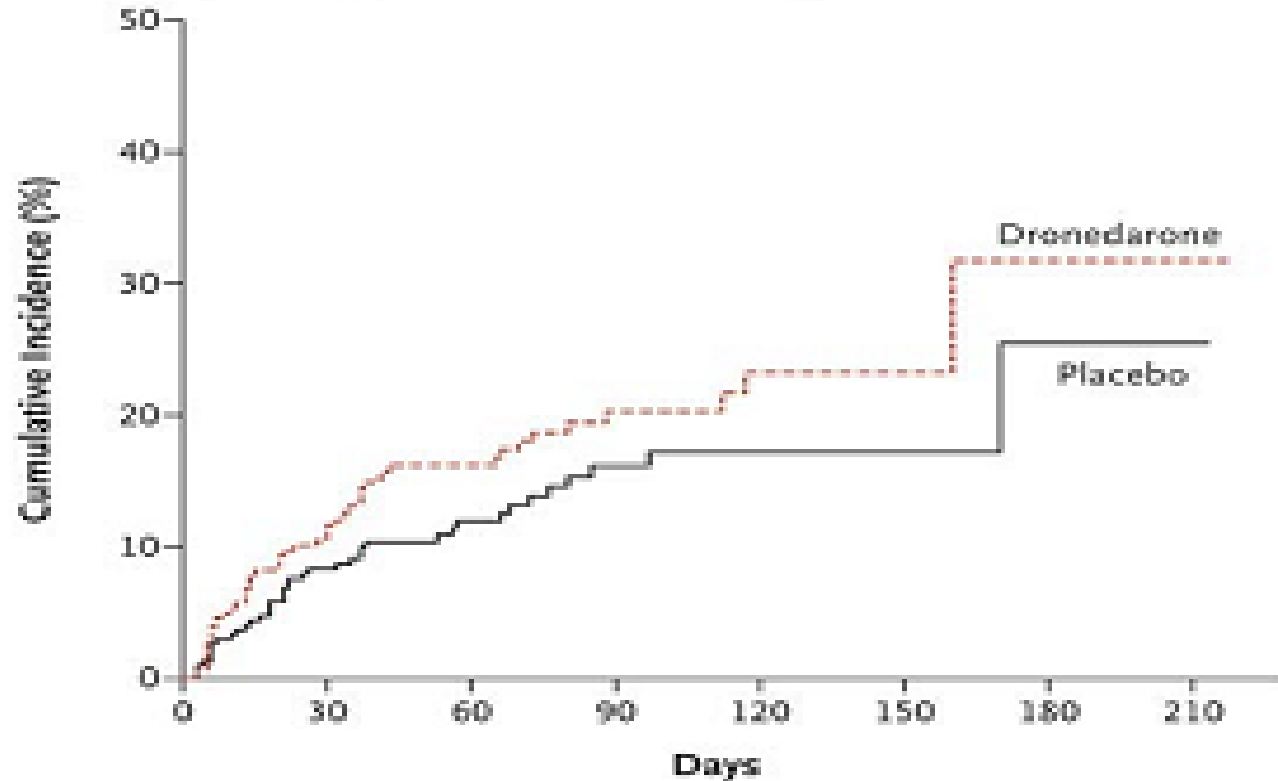
EURIDIS and ADONIS Meta-analysis

Time to First CV Hospitalization or Death



INCREASED MORTALITY AFTER DRONEDARONE THERAPY IN SEVERE HEART FAILURE (ANDROMEDA)

A All-Cause Mortality or Hospitalization for Worsening Heart Failure



No. at Risk

Placebo	317	234	159	87	41	16	6	1
Dronedaronone	310	232	151	87	49	19	4	1

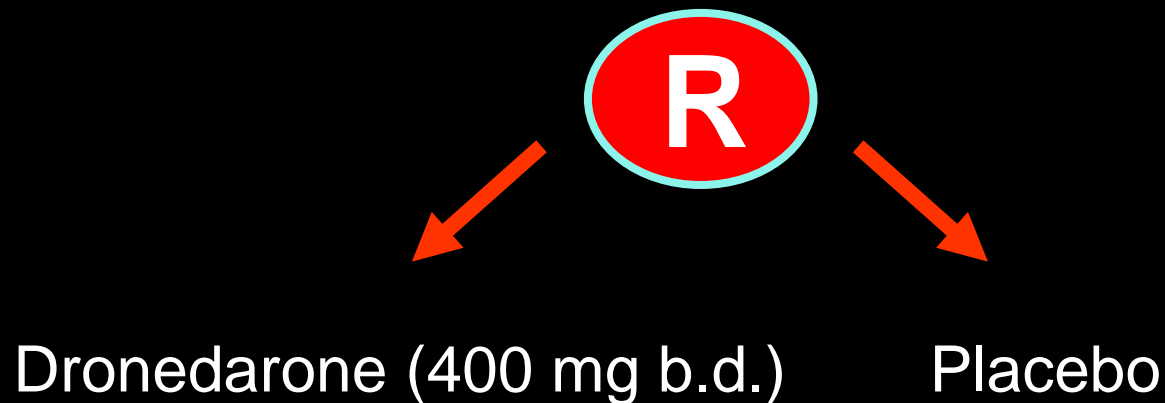
627 patients (310
Dronedaronone, 317
placebo)

Trial prematurely
terminated due to
increased mortality
related to worsening
heart failure

ATHENA Trial Design – Phase III RCT

N=4628 patients with a history of paroxysmal or persistent AF

- Age \geq 75 years with or without additional risk factors
- Age \geq 70 years and \geq 1 risk factor (hypertension, diabetes, prior stroke/TIA, LA \geq 50 mm, LVEF \leq .40)



Minimum follow-up 12 months

Primary endpoint: time to Death or Cardiovascular Hospitalization

ATHENA: Patient Characteristics

	Placebo (N=2327)	Dronedaronone (N=2301)
Age (yrs)	72+/-9	72+/-9
Female gender	45%	49%
AF at baseline	25%	25%
Structural Heart Disease	61%	58%
Hypertension	86%	87%
Coronary Heart Disease	32%	29%
Valvular Heart Disease	16%	17%
NYHA III/IV	22%	20%
EF<0.35	4%	4%
Lone AF	6%	6%

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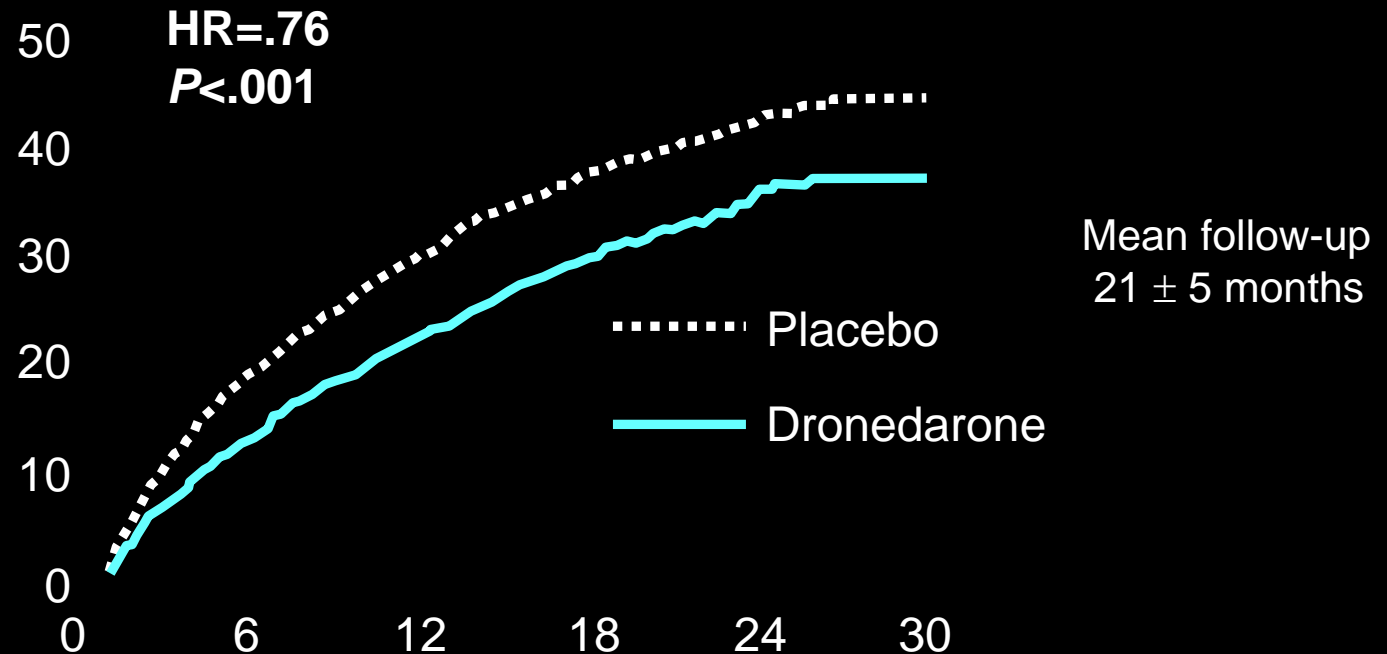
	Placebo (N=2327)	Dronedarone (N=2301)
Betablocker	71%	71%
Ca-antagonists	13%	14%
Digoxin	13%	14%
ACE/ARB	69%	70%
Statins	39%	38%
Vit.K anatagonists	60%	61%
Aspirin	44%	44%

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Aspirin	44%	44%

ATHENA - Primary Outcomes

Time to first cardiovascular hospitalization or death



Patients at risk

Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

ANNUAL STROKE RATES AND HAZARD RATIOS (HR)

DRONEDARONE VS. PLACEBO

END POINT	Placebo (%/y)	Dronedaronone (%/y)	HR (95% CI)	p
Stroke	1.79	1.19	0.66 (0.46–0.96)	0.027
Stroke or TIA	2.05	1.37	0.67 (0.47–0.94)	
Fatal stroke	0.54	0.36	0.67 (0.34–1.32)	0.247
Stroke, ACS, or CV death	5.52	3.80	0.68 (0.55–0.84)	<0.001
Stroke, ACS, or all- cause death	6.70	5.06	0.75 (0.62–0.90)	0.002

TIA=transient ischemic attack

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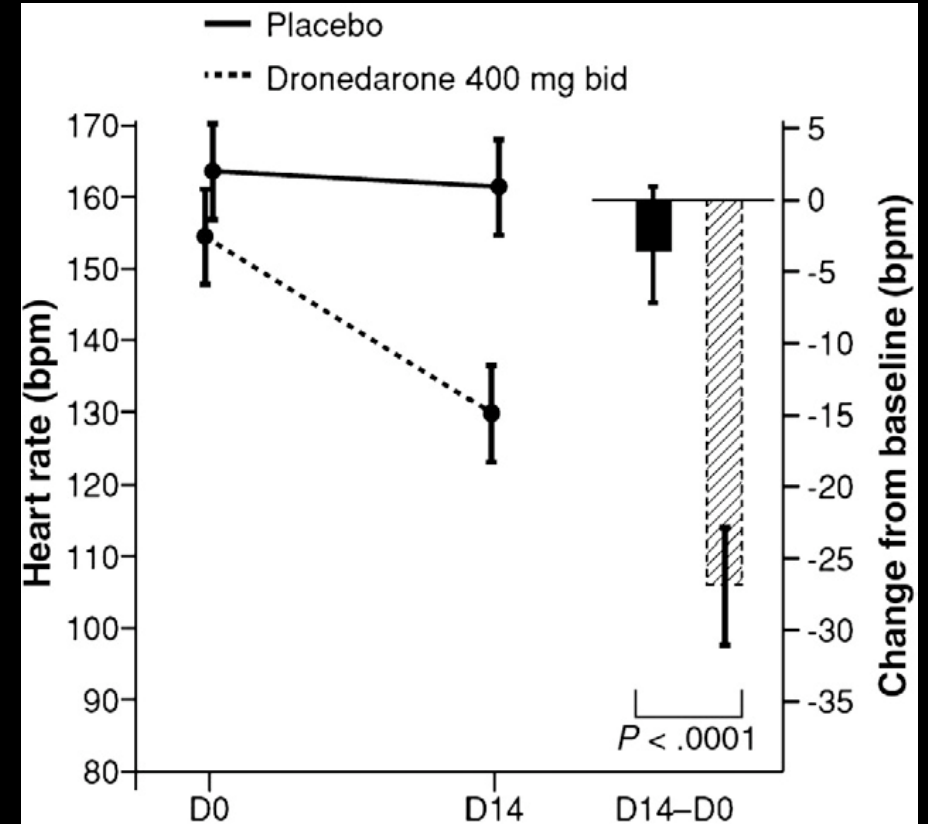
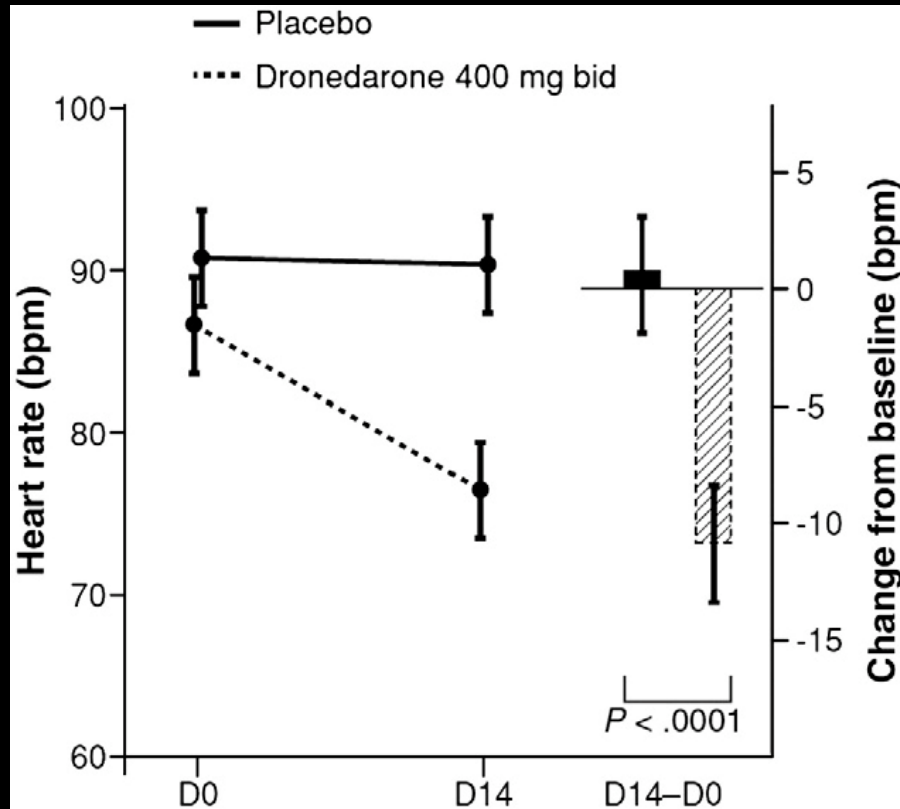
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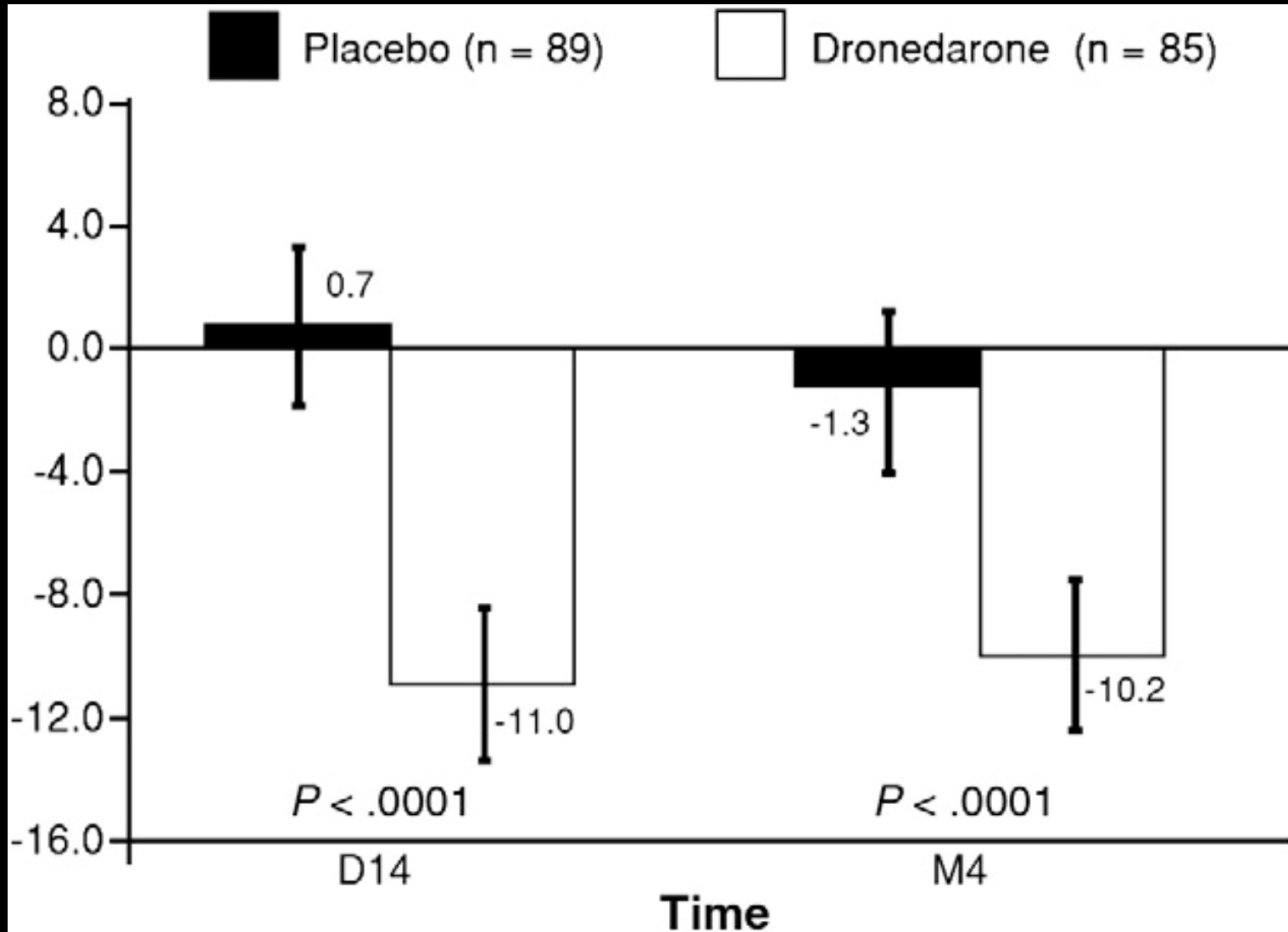
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DRONEDARONE REDUCES RESTING AND MAXIMAL HEART RATES (ERATO)



J.M. Davy *et al.* Am Heart J. 2008; 156: 527–529

DRONEDARONE REDUCES AMBULATORY HEART RATES (ERATO)



ATHENA: Summary and Consequences

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- Thursday July 2nd 2009 – FDA approval granted

MULTAQ - highlights of prescribing information (Sanofi-Aventis USA, revised July 2nd 2009)

- 'indicated to reduce the risk of cardiovascular hospitalization in patients with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e. age > 70, hypertension, diabetes) who are in sinus rhythm or will be cardioverted.'

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BLACK BOX WARNING –

- ‘....contraindicated in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation....’

**25TH SEPTEMBER 2009 MULTAQ®
(DRONEDARONE) RECOMMENDED FOR
APPROVAL IN THE EUROPEAN UNION**

‘The CHMP has recommended the approval of Multaq® in adult clinically stable patients with history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.’

Drug Targets and Atrial Fibrillation

The Next 5 Years

- **Atrial fibrillation becoming more common**
- **Greater emphasis on prevention/general prophylaxis**

Drug Targets and Atrial Fibrillation

The Next 5 Years

- **Atrial fibrillation becoming more common**
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- **New “safer” variations of conventional therapies e.g. Dronedarone almost available**
- **Drugs with many novel direct and indirect antiarrhythmic actions are in development**