Amiodarone in Pts with LV Dysfunction
How Safe Is It ?

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Friday 16 morning - Arazzi Room

08.30–09.45

Featured Symposium

Zoom in on atrial fibrillation

Program Chairmen: Andrea Natale – Antonio Raviele – Sakis Themistoclakis

DRUG PROPHYLAXIS OF AF: 2015 UPDATE

Chairmen: **A. Capucci** / Ancona, Italy - **E.N. Simantirakis** / Heraklion, Greece

Amiodarone in patients with LV dysfunction: how safe is it?
G.L. Botto / Como, Italy

Beta–blockers as preferred therapy in HF patients with AF: is it time to change?
I.C. Van Gelder / Groningen, The Netherlands

Vernakalant for cardioversion of AF: who, when, why
S. Lévy / Marseille, France

Ranalozine as a promising treatment option for AF, alone or in combination with other AADs
A.J. Camm / London, UK

Presenter Disclosure Information

- Research support:
  Boston Scientific, Medtronic; St. Jude Medical, Bayer Healthcare, Gilead, Sanofi

- Advisory Board:
  Biotronik, Medtronic; St. Jude Medical, Sorin Group, MSD, Bayer Healthcare, Boehringer, BMS/Pfizer, Sanofi

- Speaker Fees:
  Boston Scientific, Medtronic, St. Jude Medical, Sorin Group, Bayer Healthcare, Boehringer, BMS/Pfizer, Meda, MSD, Sanofi, Cardiome
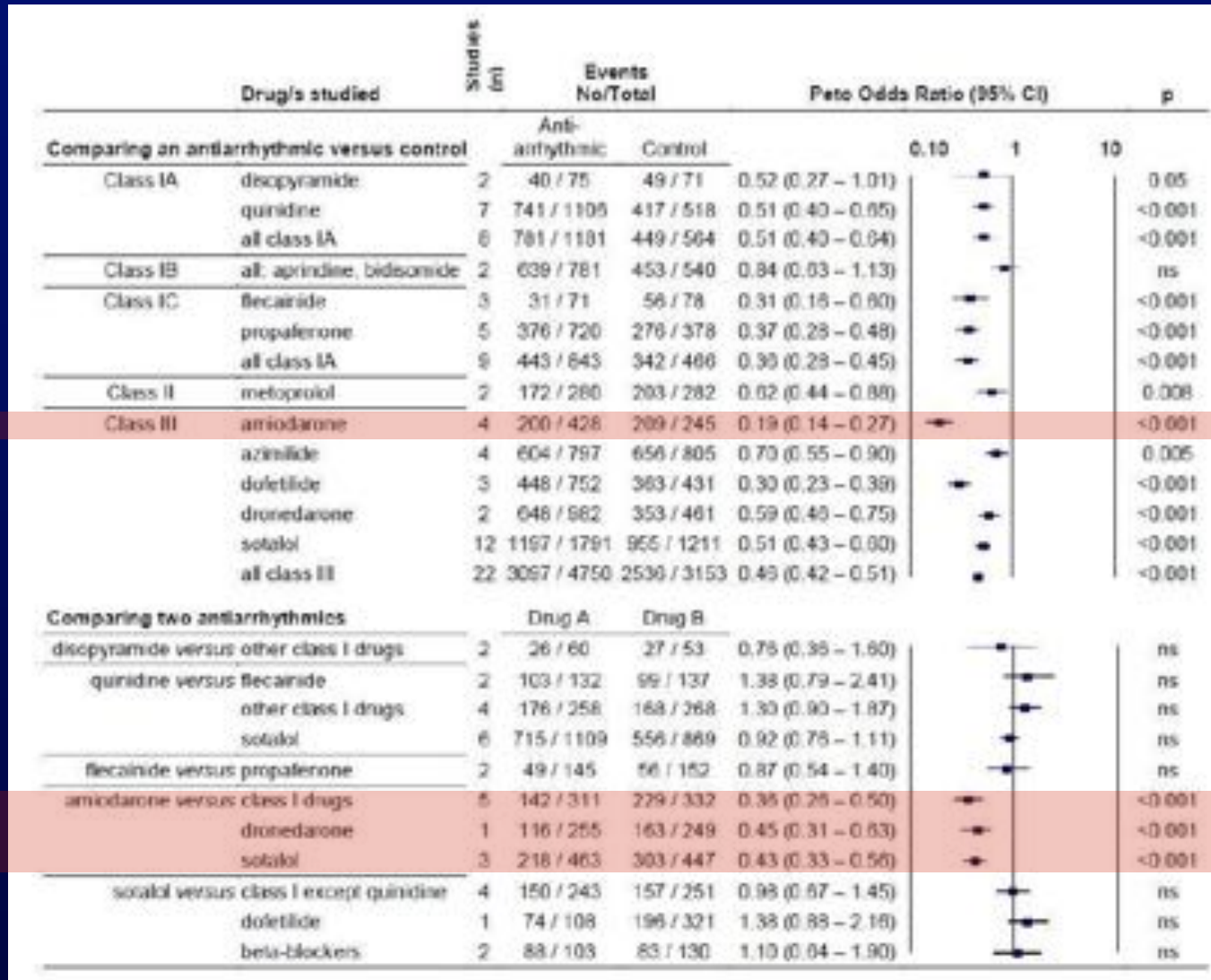
Atrial Fibrillation
Background on AADs

- Are only modestly effective in maintaining SR
- Have potential for serious or letal adverese events
- Have had few studies with long-term follow-up or meaningful mortality statistics

If antiarrhythmic drugs had adequate clinical efficacy and safety, there probably would never had been any rate vs rhythm control trial

AADs for Maintaining SR After CV of AF
Effect on Maintanance of SR

Drug/s studied		Studies (n)	Events No/Total		Peto Odds Ratio (95% CI)	p
			Anti-arrhythmic	Control		
Comparing an antiarrhythmic versus control						
Class IA	disopyramide	2	40 / 75	49 / 71	0.52 (0.27 – 1.01)	0.05
	quinidine	7	741 / 1106	417 / 518	0.51 (0.40 – 0.65)	<0.001
	all class IA	8	781 / 1181	449 / 564	0.51 (0.40 – 0.64)	<0.001
Class IB	all: aprindine, bidisomide	2	639 / 781	453 / 540	0.84 (0.63 – 1.13)	ns
Class IC	flecainide	3	31 / 71	56 / 78	0.31 (0.16 – 0.60)	<0.001
	propafenone	5	376 / 720	276 / 378	0.37 (0.28 – 0.48)	<0.001
	all class IA	9	443 / 843	342 / 466	0.36 (0.28 – 0.45)	<0.001
Class II	metoprolol	2	172 / 280	203 / 282	0.62 (0.44 – 0.88)	0.008
Class III	amiodarone	4	200 / 428	209 / 245	0.19 (0.14 – 0.27)	<0.001
	azimilide	4	604 / 797	656 / 805	0.70 (0.55 – 0.90)	0.005
	dofetilide	3	448 / 752	383 / 431	0.30 (0.23 – 0.39)	<0.001
	dronedarone	2	646 / 982	353 / 461	0.59 (0.46 – 0.75)	<0.001
	sotalol	12	1197 / 1791	955 / 1211	0.51 (0.43 – 0.60)	<0.001
	all class III	22	3097 / 4750	2536 / 3153	0.46 (0.42 – 0.51)	<0.001
Comparing two antiarrhythmics			Drug A	Drug B		
disopyramide versus other class I drugs		2	26 / 60	27 / 53	0.76 (0.36 – 1.60)	ns
quinidine versus flecainide		2	103 / 132	99 / 137	1.38 (0.79 – 2.41)	ns
	other class I drugs	4	176 / 256	168 / 268	1.30 (0.90 – 1.87)	ns
	sotalol	6	715 / 1109	556 / 869	0.92 (0.76 – 1.11)	ns
flecainide versus propafenone		2	49 / 145	56 / 152	0.87 (0.54 – 1.40)	ns
amiodarone versus class I drugs		6	142 / 311	229 / 332	0.36 (0.26 – 0.50)	<0.001
	dronedarone	1	116 / 255	163 / 249	0.45 (0.31 – 0.63)	<0.001
	sotalol	3	218 / 463	303 / 447	0.43 (0.33 – 0.56)	<0.001
sotalol versus class I except quinidine		4	150 / 243	157 / 251	0.98 (0.67 – 1.45)	ns
	dofetilide	1	74 / 108	196 / 321	1.38 (0.88 – 2.16)	ns
	beta-blockers	2	88 / 103	83 / 130	1.10 (0.64 – 1.90)	ns

Amiodarone in 5060 AF Patients
Meta-analysis

8 studies compared A with a rate control drug, either beta-blocker or digoxin
4 trials compared A with placebo.

Outcome of Interest	Relative Risk [95% CI]	p-value (test for overall effect)
Conversion to sinus rhythm per patients-year follow up	3.22 [1.88–5.53]	<0.0001
Incidence of all-cause mortality per patient-year follow up	0.95 [0.81–1.11]	0.51
Rate of all-cause hospitalisation per patients-year follow up	1.10 [0.57–2.13]	0.77

Conversion/maintenance of SR is NOT associated with a reduction of all-cause death or all-cause hospitalisation

Doyle JFD. *Mayo Clin Proc.* 2009; 84: 234-242.

Rate or Rhythm in AFIB
Randomized Controlled Trials

PIAF N=252	AFFIRM N=4060	RACE N=522	STAF N=200	HOTCAFE N=205
Persistent 7 d to 1 y	Paroxysmal & Persistent	Persistent Recurrent after ECV	Persistent > 4 w ECV needed	Persistent 7 d to 2 y First Episode ECV needed
60 y-o	70 y-o	68 y-o	65 y-o	61 y-o
16% lone	13% lone	21% lone	11% lone	21% lone
Few HF	23% HF	50% HF	45% HF	62% HF

Time-Dependent Co-variates Associates with Survival

On Treatment Analysis

	p Value	Hazard Ratio	99% CI
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
AADs use	=0.0005	1.49	1.11-2.01

HR <1.00: decreased risk of sudden death
HR >1.00: increased risk of sudden death

The AFFIRM Investigators
Circulation 2004; 109: 1509-1513

AFFIRM

Atrial Fibrillation Follow-up Investigation of Rhythm Management
Comparative Use of Drugs For Initial Rx

Wyse G. Late-breaking session ACC 2002
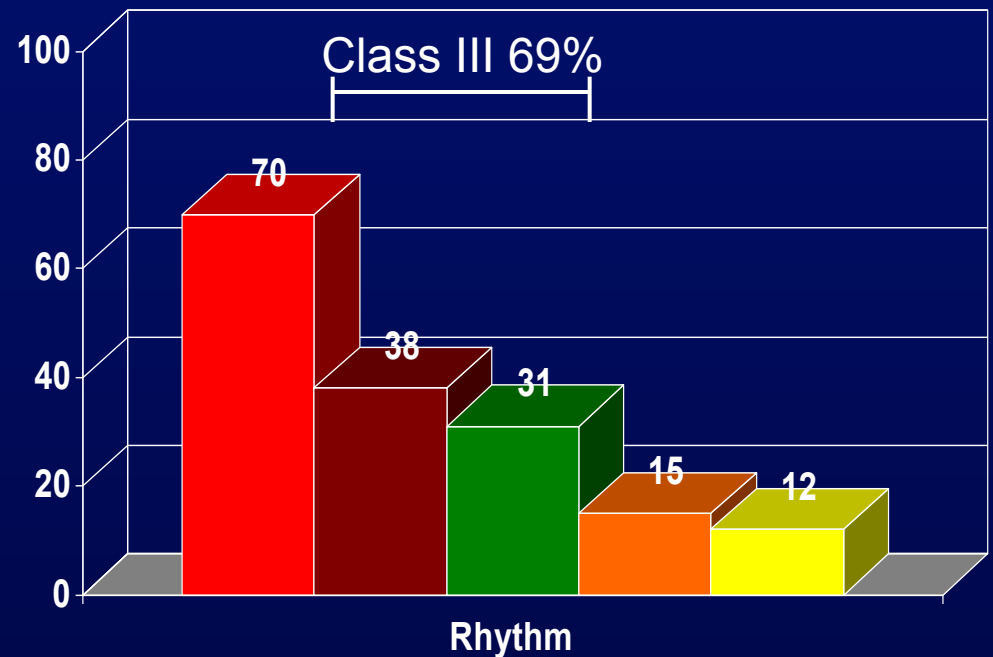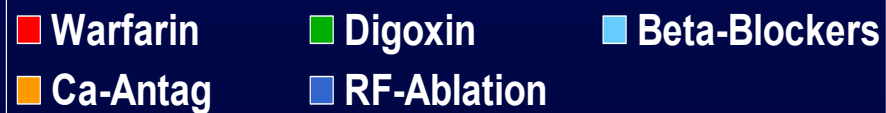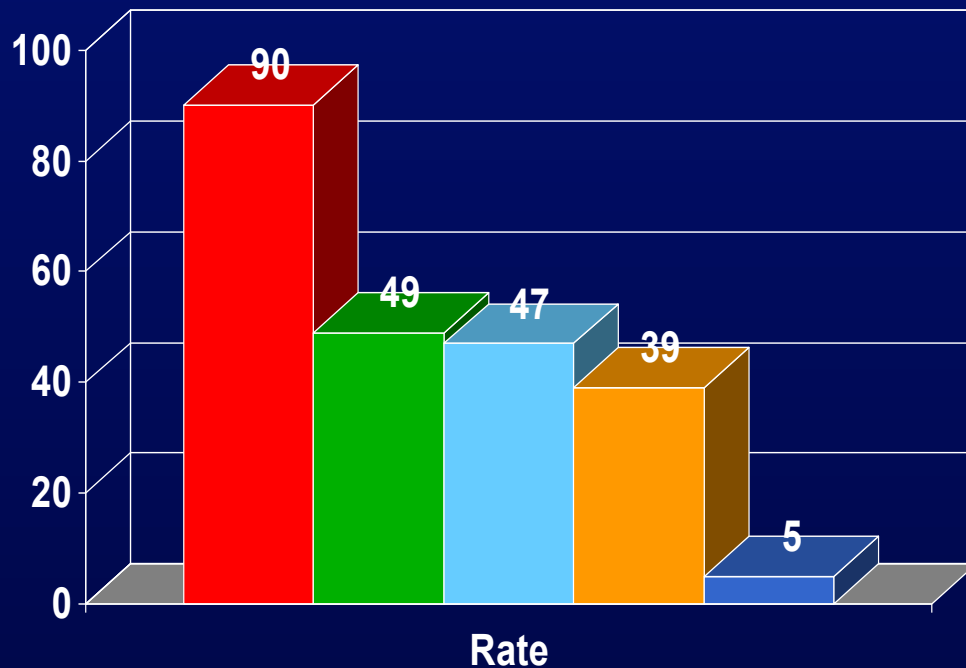
AFFIRM
Comparison of Cause-Specific Mode of Death

	Rate (N=2027)	Rhythm (N=2033)	P Value
Total Deaths	310	356	0.078
Cardiac	130	129	0.95
Vascular	37	35	0.82
Non-CV	113	169	0.0008
Uncertain	30	23	0.34

Steimberg JS. Circul 2004; 109: 1973-1980

AFFIRM Study
Risk of Pro-Arrhyhtmic Events

3030 exposures to ADDs in 2033 pts
96 AEs in 6-y F-U

- 3,16% in 6-y
- 0,53% per year

The overall risk of adverse arrhythmic events upon exposure to AADs in the AFFIRM study is reasonably low

N, Events (%)

Female :	405, 0 (100)	383, 4 (1)	363, 6 (2)	276, 8 (2)	174, 12 (4)	55, 14 (5)
Male :	642, 0 (100)	629, 4 (1)	591, 9 (1)	446, 15 (3)	271, 21 (4)	95, 23 (5)

Kaufman ES. JACC 2004; 44: 1276-82
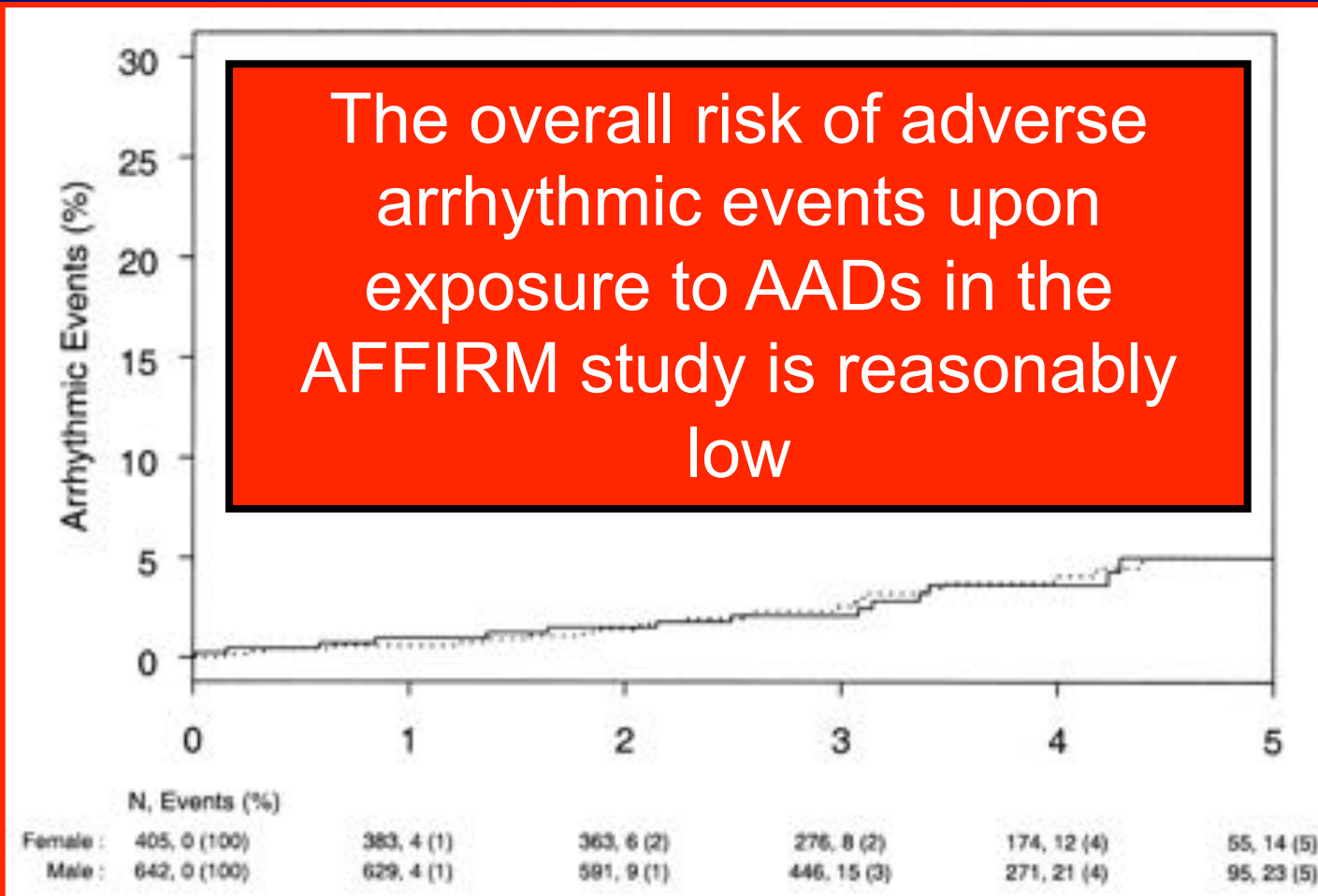
AFFIRM
Non-Cardiovascular Mode of Death

	Rate (N=2027)	Rhythm (N=2033)	P Value
Total Non-CV	113	169	0.0008
Cancer	52	81	0.01
Pulmonary	23	39	0.04
Sepsis	12	12	NS
Other	26	37	NS

Steinberg JS. Circul 2004; 109: 1973-1980

Comparison of Non-Cardiovascular Mode of Death
AFFIRM

Non-CardioVascular

Cancer

Pulmunary

Steimberg JS.
Circul 2004;
109: 1973-1980
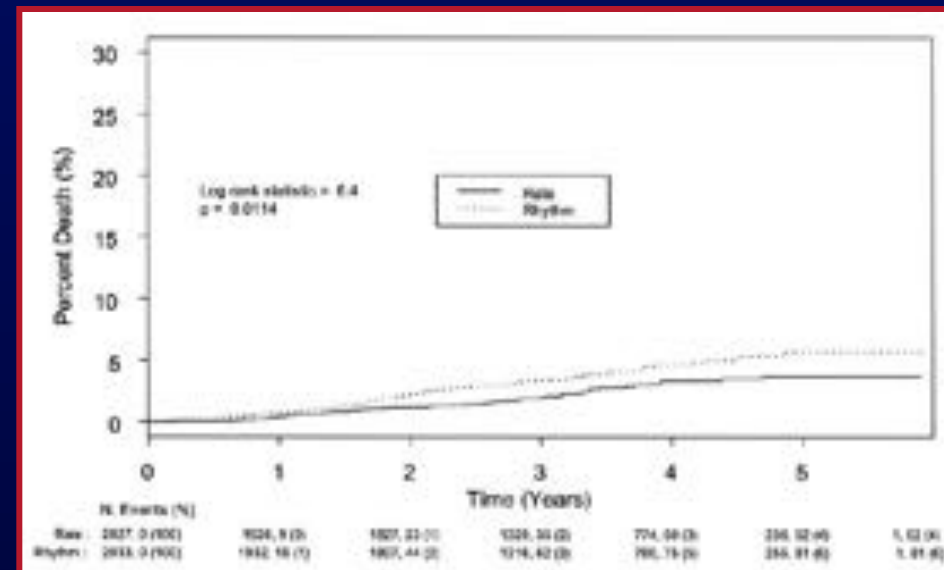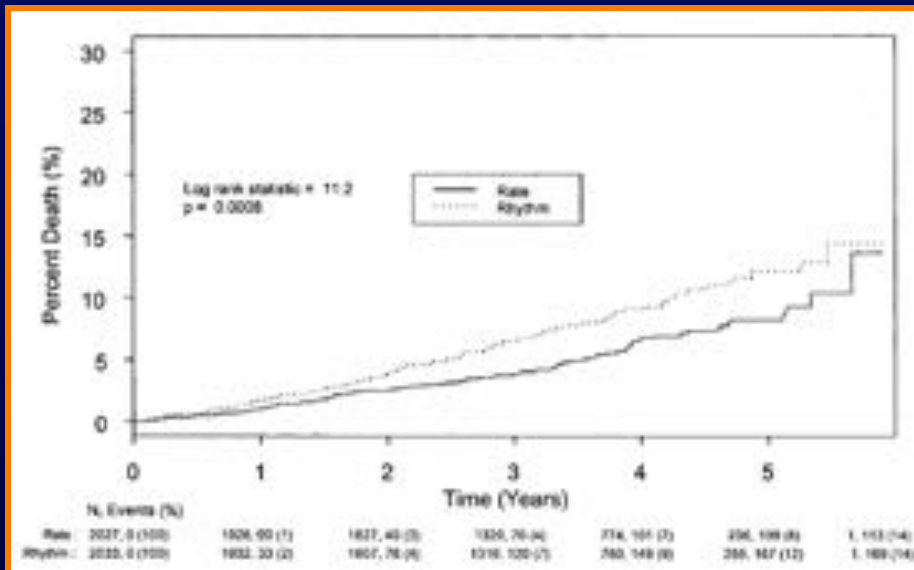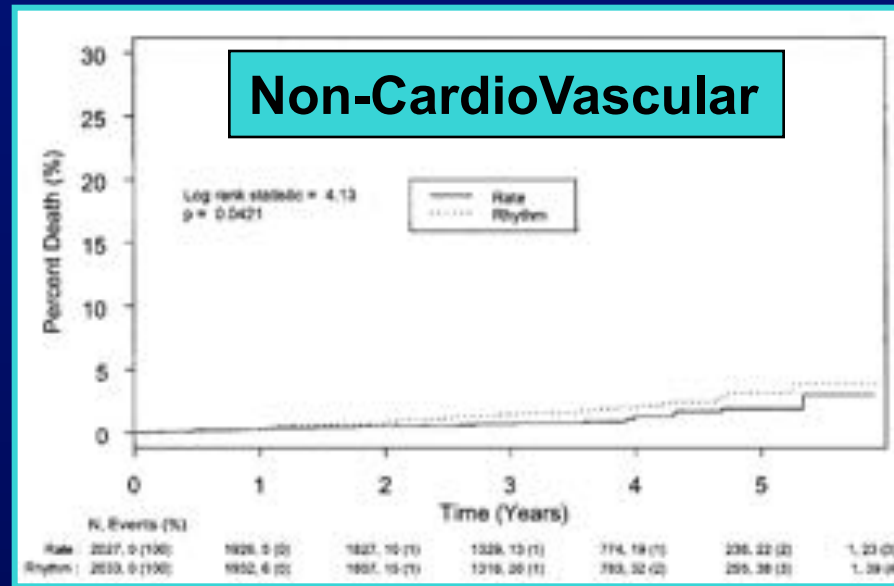
ATMA Study
Side Effects Causing Early Drop-out

	AMIO (%)	Placebo (%)	OR
Hypothiroidism	181/2580 (7.0)	27/2545 (1.1)	7.3
Hyperthiroidism	37/2580 (1.4)	13/2545 (0.5)	2.5
Peripheric neuropathy	12/2580 (0.5)	4/2545 (0.2)	2.8
Pulmonary infiltrates	42/2580 (1.6)	12/2545 (0.5)	3.1
Bradycardia	44/2580 (2.4)	19/2545 (0.8)	2.6
Liver dysfunction	26/2580 (1.0)	9/2545 (0.4)	2.7

Amiodarone Trials Meta-Analysis Investigators. *Lancet* 350:1417; 1997

DL-Co Modification @ 1-Y follow-up in Amiodarone Treated Pts
Data From CHF-STAT

J Am Coll Cardiol 1997; 30: 514-517
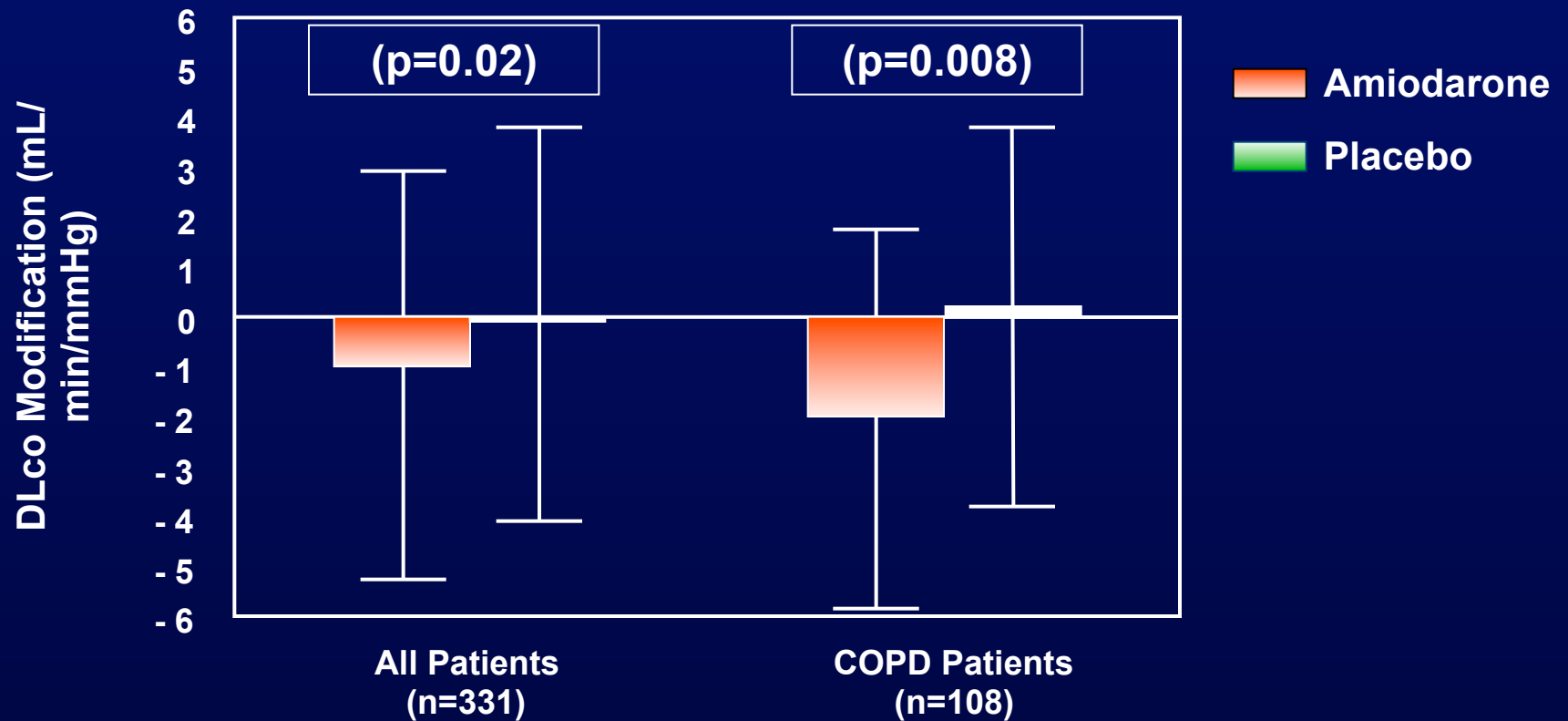
Amiodarone Pulmunary Toxicity
DL-Co Modification
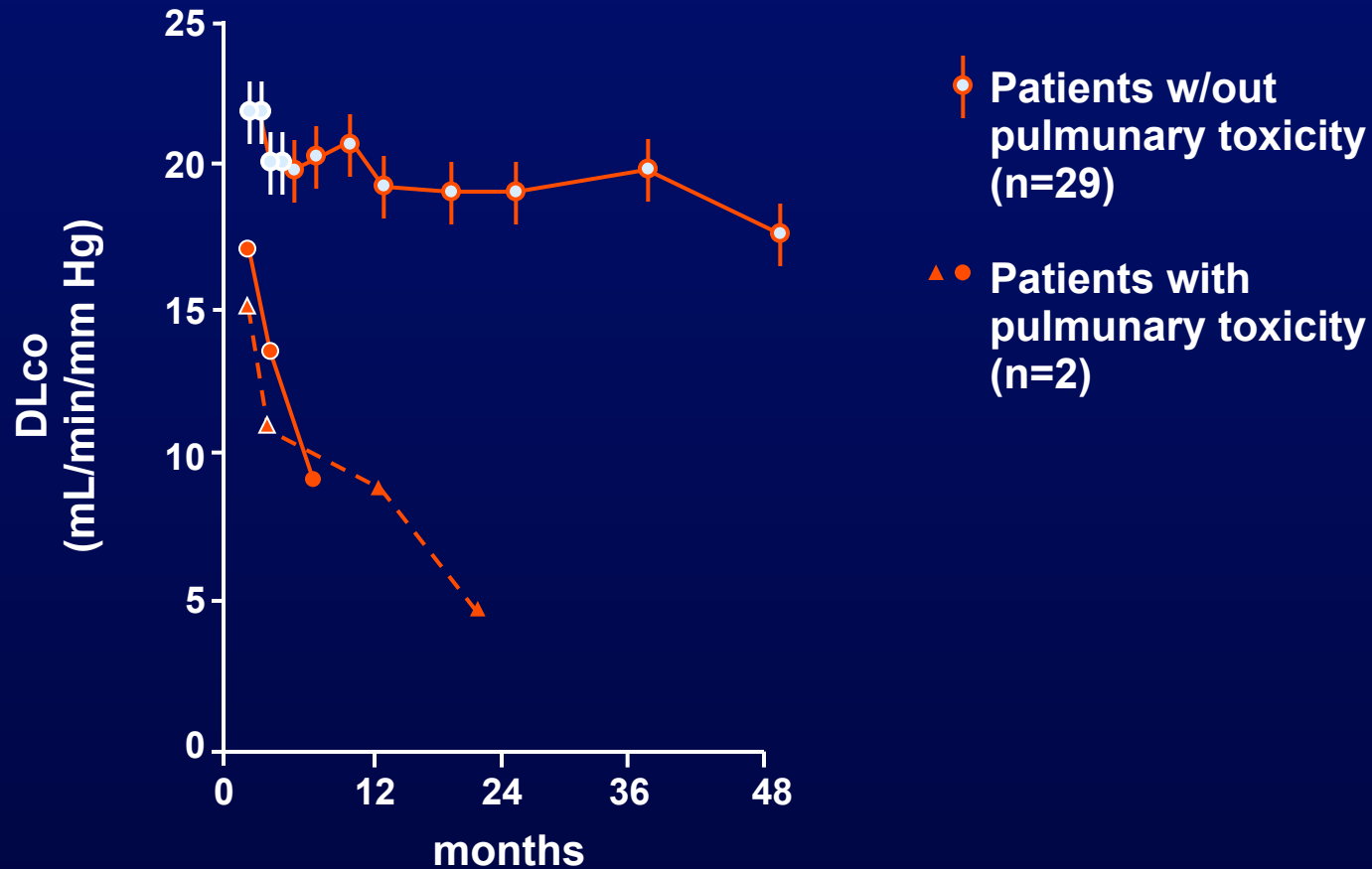
AFFIRM
Atrial Fibrillation Follow-up Investigation of Rhythm Management
Amiodarone & Pulmonary Disease

Olshansky B. Am J Cardiol 2005; 94: 405-405
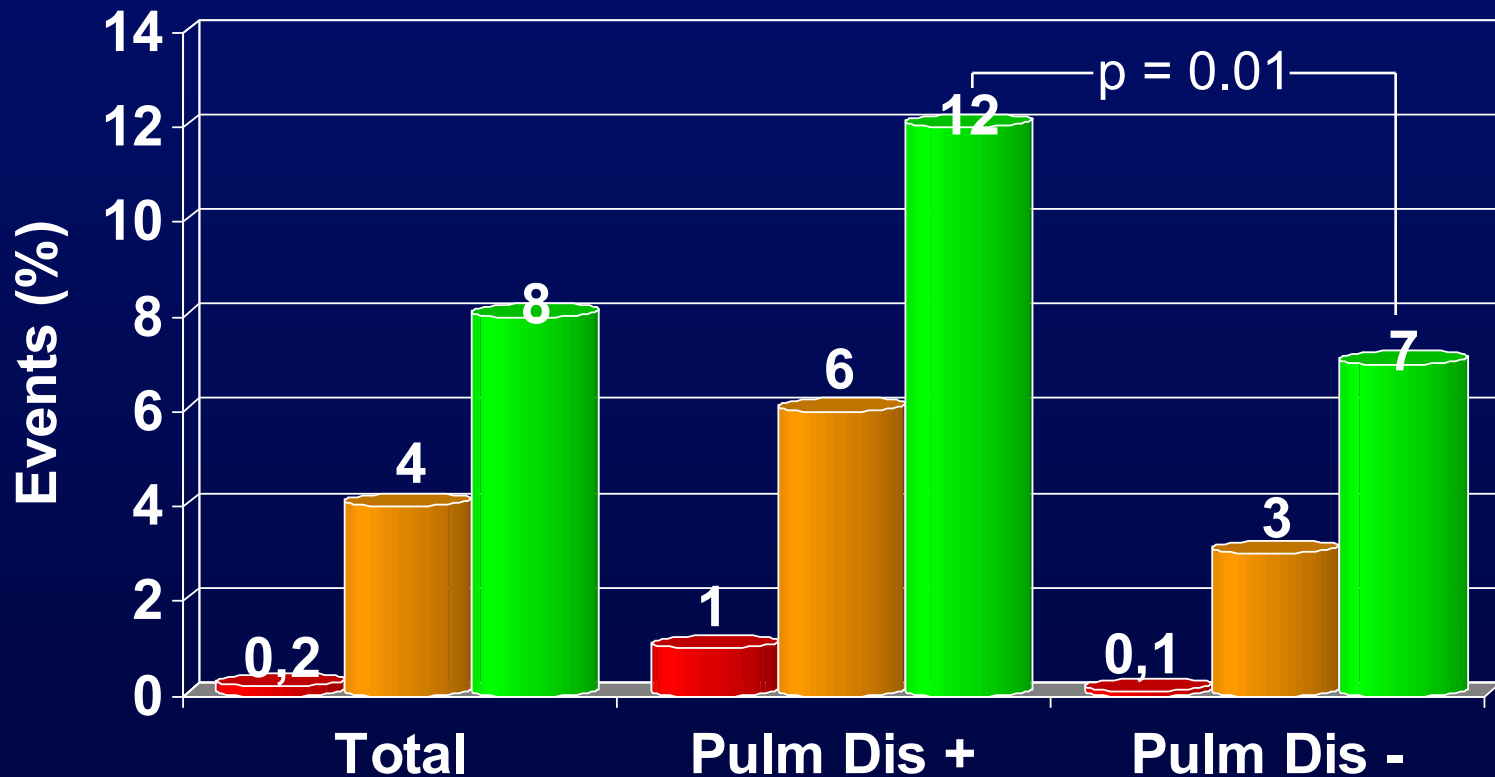
Amiodarone and the Risk of Cancer

A Nationwide Population-Based Study

Vincent Yi-Fong Su, MD[1]; Yu-Wen Hu, MD[2,3,4]; Kun-Ta Chou, MD[1,3]; Shuo-Ming Ou, MD[5]; Yu-Chin Lee, PhD[1,3]; Elizabeth Ya-Hsuan Lin, BSc[6]; Tzeng-Ji Chen, PhD[3,7]; Cheng-Hwai Tzeng, PhD[3,8]; and Chia-Jen Liu, MD[3,4,8,9]

Variables	Univariate Analysis HR (95% CI)	P	Multivariate Analysis[a] HR (95% CI)	P
Age[b]	1.04 (1.03-1.06)	<.001	1.04 (1.03-1.06)	<.001
Male sex	1.98 (1.45-2.72)	<.001	1.90 (1.38-2.62)	<.001
Diabetes mellitus	1.11 (0.81-1.51)	.524		
Cirrhosis	3.81 (2.16-6.69)	<.001	3.70 (2.10-6.52)	<.001
COPD	1.15 (0.85-1.56)	.364		
Chronic kidney disease	1.04 (0.69-1.55)	.856		
Heart failure	0.96 (0.72-1.30)	.807		
Hypertension	1.24 (0.91-1.69)	.180		
Cardiovascular disease	0.99 (0.74-1.33)	.961		
Hyperthyroidism	0.25 (0.06-0.99)	.048	0.33 (0.08-1.35)	.123
Hypothyroidism	0.05 (0.00-20.57)	.328		
SES (mo income, NTD)[c]				
20,000-39,999	0.51 (0.37-0.70)	<.001	0.63 (0.45-0.87)	.006
≥40,000	0.52 (0.34-0.78)	.002	0.62 (0.41-0.94)	.024
Urbanization[d]				
Intermediate	0.77 (0.50-1.18)	.227		
High	0.75 (0.51-1.12)	.160		
cDDDs[e]	1.001 (1.000-1.002)	.008	1.001 (1.000-1.002)	.022

cumulative defined daily doses (cDDDs) (≤ 103, 103-253, and > 253) of amiodarone

Low
Intermediate
High

Log rank p = 0.023

Cumulative incidence of cancer (%)

Follow-up (years)
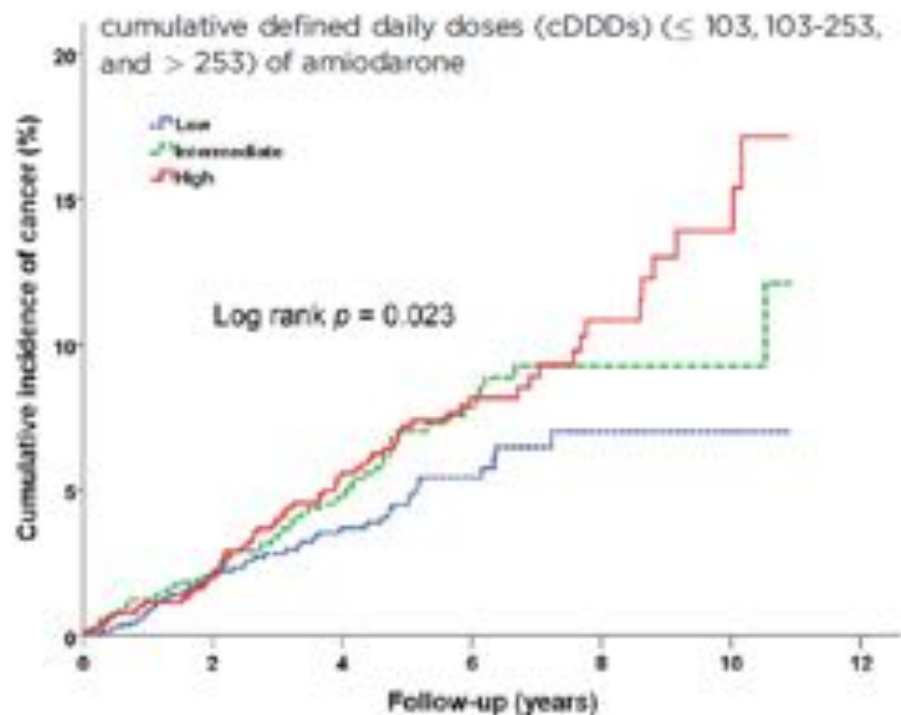
Mortality Risk Of Long-term Amiodarone Therapy For AF Pts W/out Structural HD

Prescribers of 1st AADs

	AMIO	NON-AMIO	Total
Primary Care Physician (%)	39 (30.7)	88 (69.3)	127
General Cardiologist (%)	227 (21.7)	820 (78.3)	1047
Electrophysiologist (%)	47 (8.9)	482 (91.1)	529
Total	313	1,390	1,703

Overall Survival for AMIO group vs. NON-AMIO group in propensity-matched cohort.

Major Clinical Outcomes for AMIO group vs. NON-AMIO group

	Propensity-matched cohort		Complete cohort	
	Hazard Ratio	P value	Hazard Ratio	P value
All-cause Mortality	2.41	0.012	2.13	0.009
Cardiac Mortality	1.40	0.527	1.75	0.293
Non-cardiac Mortality	3.55	0.008	2.25	0.021
AF Recurrence	0.93	0.574	0.88	0.227
Stroke	0.73	0.451	0.82	0.622
Cardiac Admission	1.13	0.469	1.02	0.870
AF Admission	1.00	0.996	0.89	0.478

Dingxin Qin et al. 2015

All Cause Mortality in RCT on AFIB
Trials > 100 Subjects Per Group, And ≥1 Event per Group

Dronedarone — 0.85 (0.67, 1.09) P=0.165

Amiodarone — 2.73 (1.00, 7.41) P=0.049

Sotalol — 4.32 (1.59, 11.70) P=0.013

0.5 1 2 5 10 100
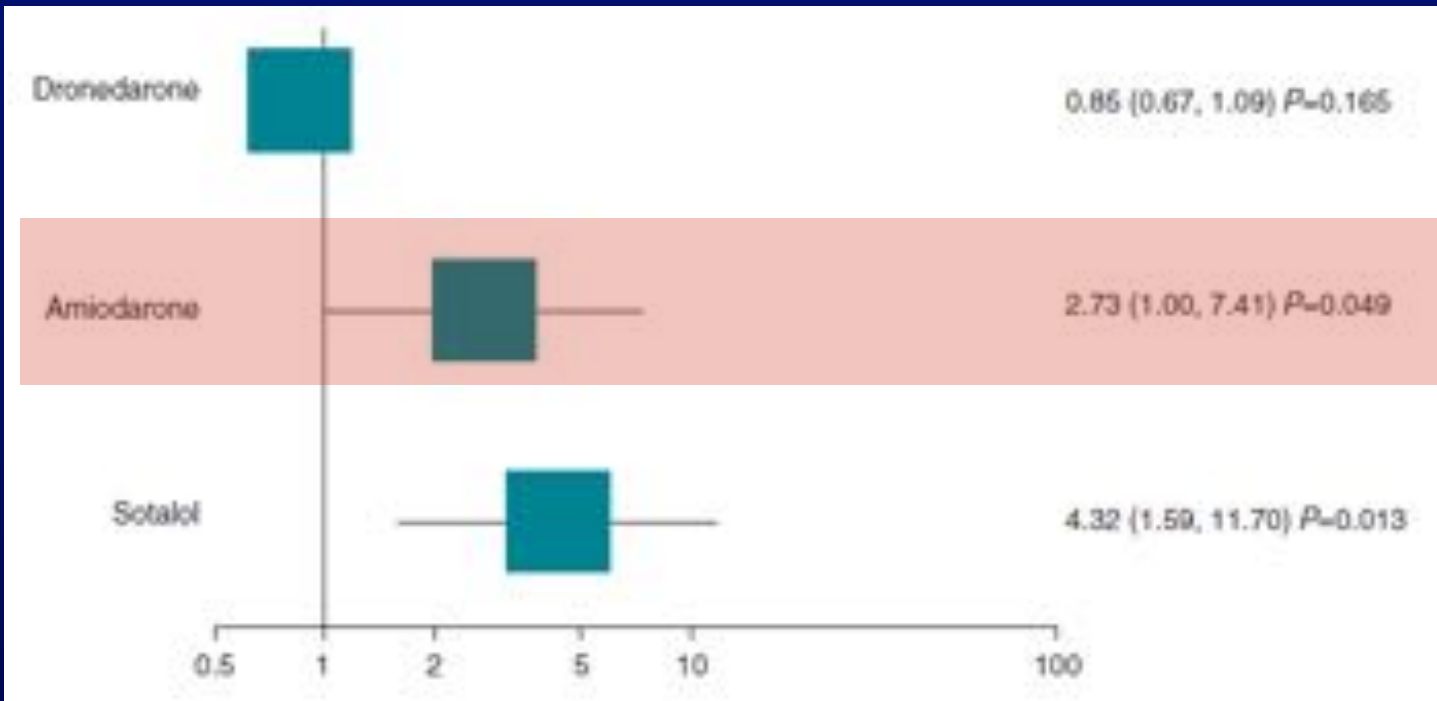
8 trials
8252 patients
349 deaths

Between Trial Heterogeneity P = 0.12

A-COMET-II, 2006
ADONIS, 2007
AFFIRM substudy, 2003
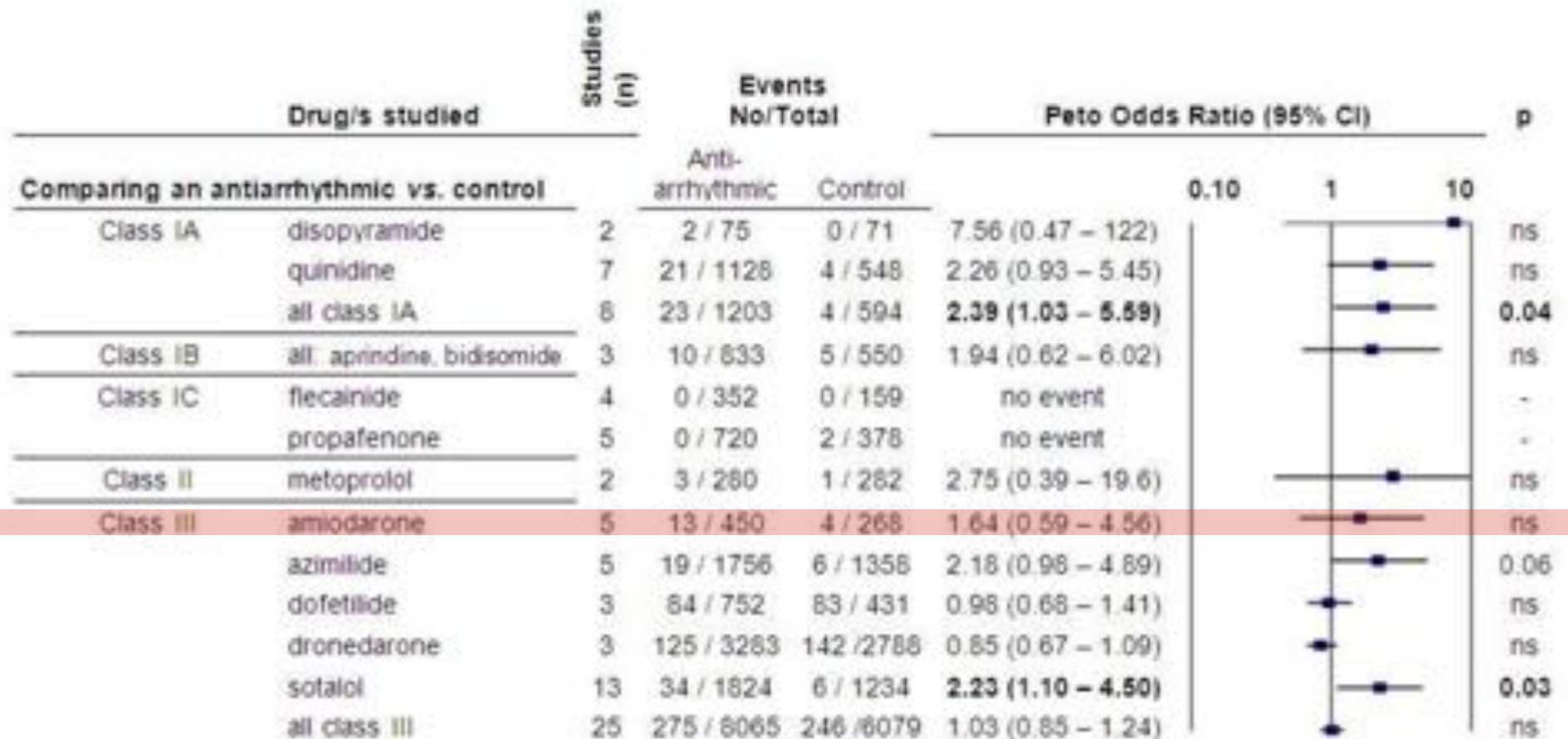ATHENA, 2009
DIONYSOS, 2009
EURIDIS, 2007
SAFE-T, 2003
SOPAT, 2004

Compared with dronedarone	Odds Ratio	Lower 95% CI	Upper 95% CI	p value
amiodarone	3.191	1.163	8.758	0.032
sotalol	5.051	1.839	13.871	0.009
placebo	1.170	0.913	1.498	0.165

Freemantle N.
Europace 2011

AADs for Maintaining SR After Cardioversion of AF
Effect on Overall Mortality

Drug/s studied		Studies (n)	Events No/Total		Peto Odds Ratio (95% CI)	p
			Anti-arrhythmic	Control		
Comparing an antiarrhythmic vs. control						
Class IA	disopyramide	2	2 / 75	0 / 71	7.56 (0.47 – 122)	ns
	quinidine	7	21 / 1128	4 / 548	2.26 (0.93 – 5.45)	ns
	all class IA	8	23 / 1203	4 / 594	**2.39 (1.03 – 5.59)**	**0.04**
Class IB	all: aprindine, bidisomide	3	10 / 833	5 / 550	1.94 (0.62 – 6.02)	ns
Class IC	flecainide	4	0 / 352	0 / 159	no event	-
	propafenone	5	0 / 720	2 / 378	no event	-
Class II	metoprolol	2	3 / 280	1 / 282	2.75 (0.39 – 19.6)	ns
Class III	amiodarone	5	13 / 450	4 / 268	1.64 (0.59 – 4.56)	ns
	azimilide	5	19 / 1756	6 / 1358	2.18 (0.98 – 4.89)	0.06
	dofetilide	3	84 / 752	83 / 431	0.98 (0.68 – 1.41)	ns
	dronedarone	3	125 / 3283	142 / 2788	0.85 (0.67 – 1.09)	ns
	sotalol	13	34 / 1824	6 / 1234	**2.23 (1.10 – 4.50)**	**0.03**
	all class III	25	275 / 8065	246 / 6079	1.03 (0.85 – 1.24)	ns

Lafuente-Lafuente C. *The Cochrane Library* 2015, Issue 3

All Cause of Death in The SCD-HeFT
Class NYHA III Patients

Bardy GH. NEJM 2055: 352: 225-237
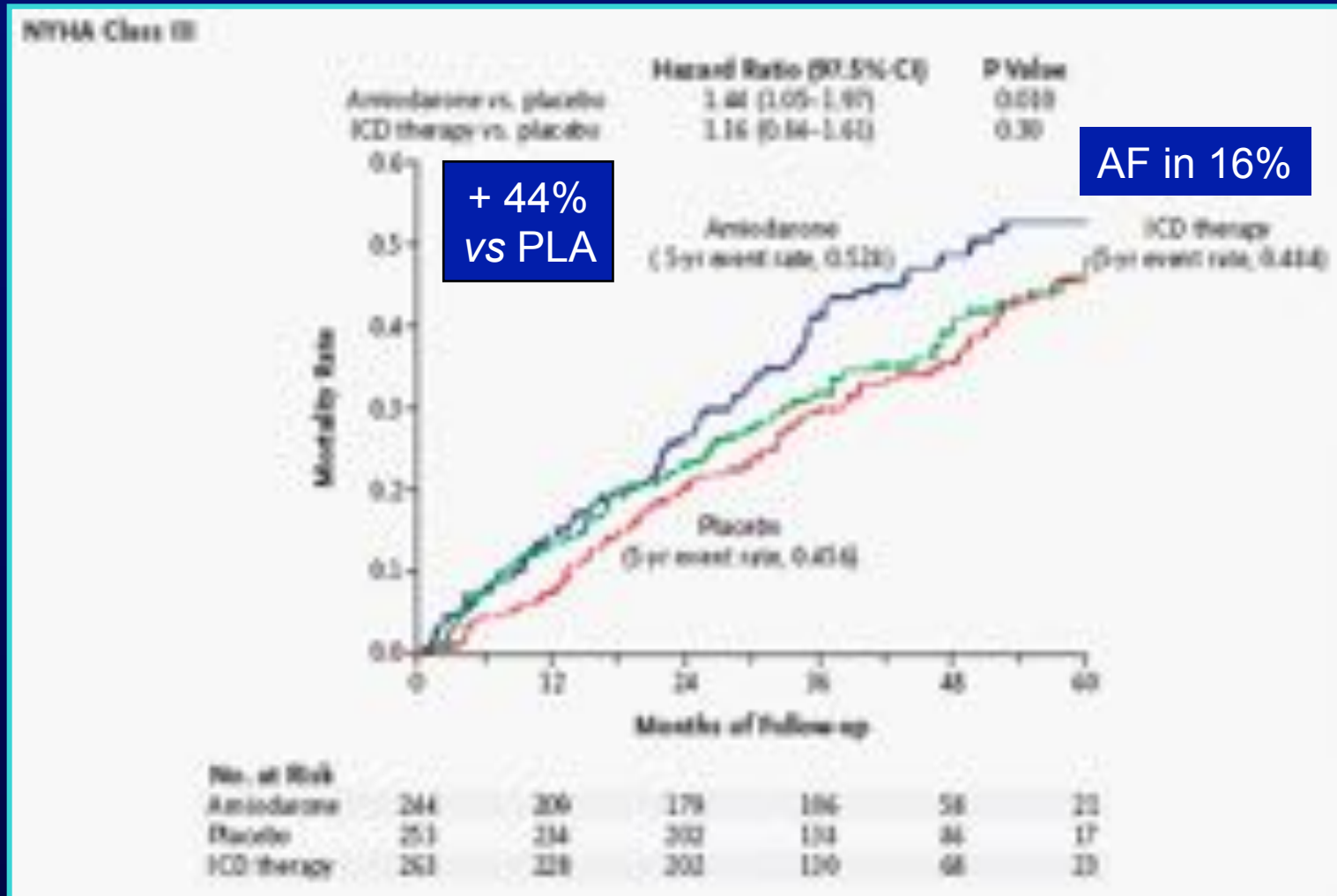
Safety of Amiodarone in HF
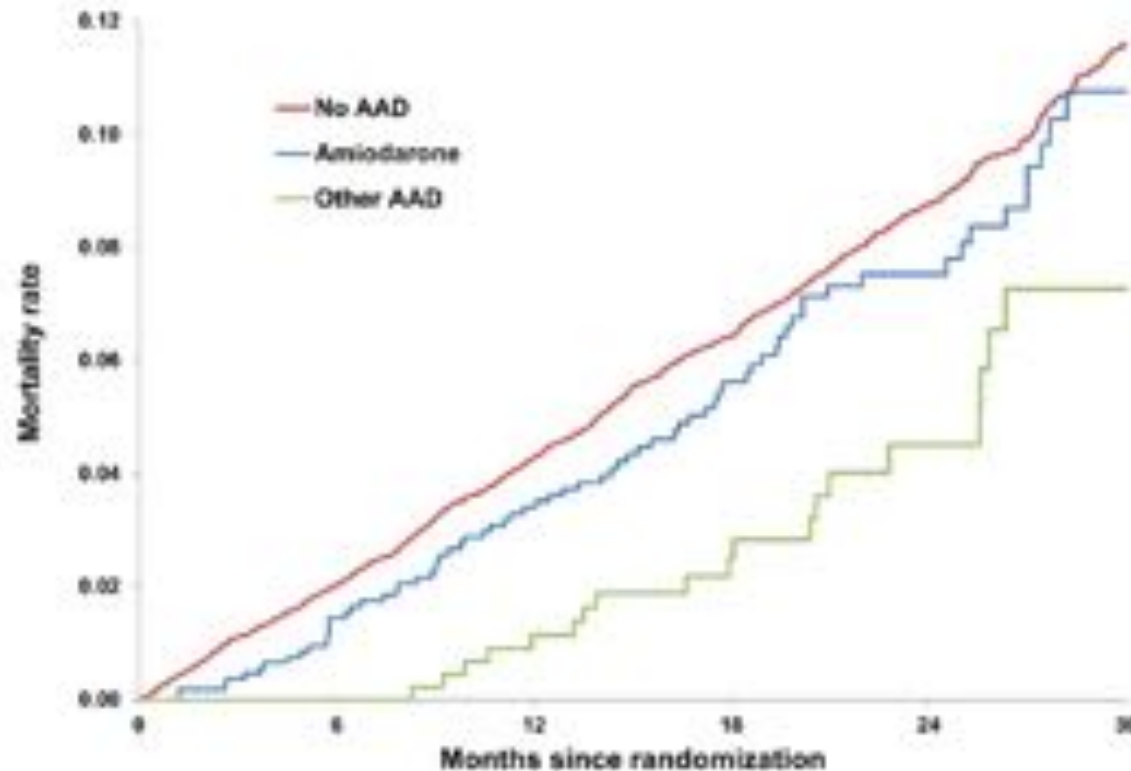## *Data From The COMET Trial*

3029 pts with CHF to carvedilol or metoprolol
Median F-U 58 mos
AF in 19,8% of pts
Amio in 12% of pts and Digitalis in 59,4% of pts

All cause mortality

Torp-Pedersen C. for the COMET Investigators. J Cardiac Fail 2007: 13: 340-345
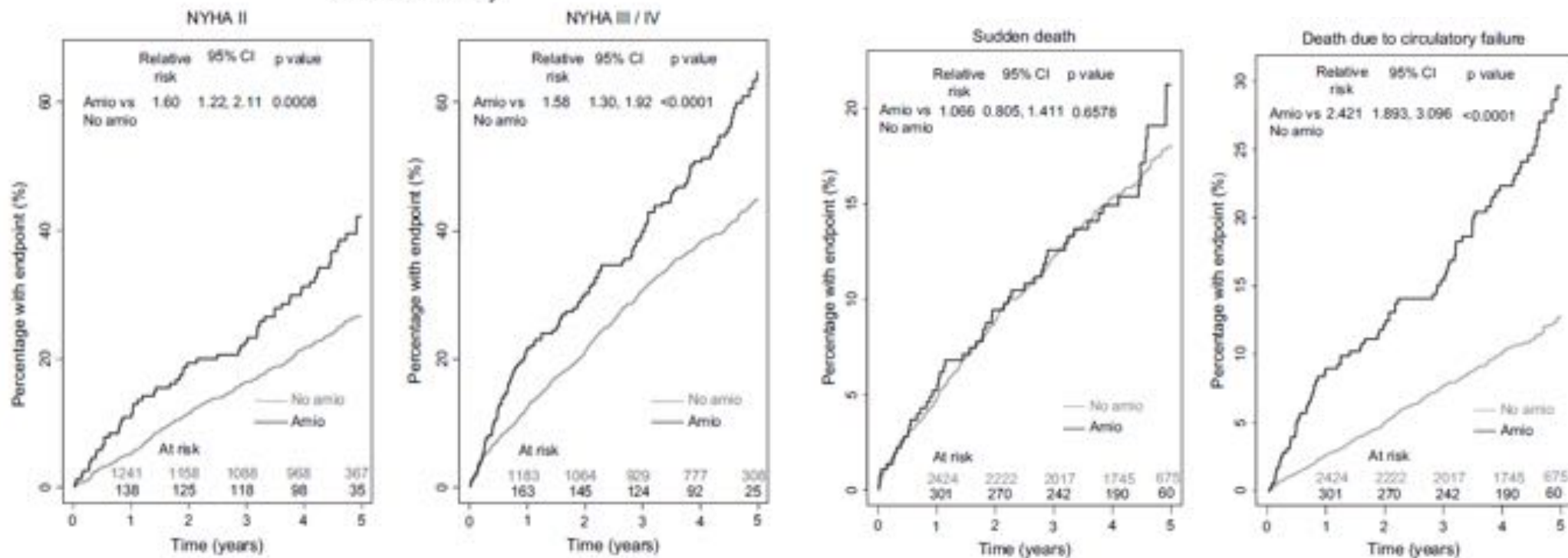
Outcomes of AAD Therapy in Pts with AF Receiving Oral Anticoagulation
Results from the ROCKET-AF trial

HF in
- 71% amio
- 41% other AADs
- 63% no AADs

Steinberg BA. Heart Rhythm 2014; 11: 925–932

Rhythm Control vs Rate Control for AF and HF
The AF-CHF Trial

Age		66±11
NYHA III-IV		76%
CAD		48%
LVEF		27±6
AFIB	Par	32%
	Per	68%
QRSd		114±30
LA		49±7

Roy D. N Engl J Med 2008; 358: 2667

Baseline Characteristics of the Patients.*

| Variable	Rhythm-Control Group (N = 682)	Rate-Control Group (N = 694)
Male sex (%)	78	85
Age (yr)	66±11	67±11
Body-mass index†	27.8±5.4	28.0±5.1
Nonwhite race (%)‡	16	13
NYHA class III or IV (%)		
At baseline	32	31
During previous 6 mo	76	76
Predominant cardiac diagnosis (%)§		
Coronary artery disease	48	48
Valvular heart disease	5	5
Nonischemic cardiomyopathy	36	39
Congenital heart disease	1	1
Hypertensive heart disease	10	7
Coexisting conditions (%)		
Hypertension	49	46
Diabetes	22	20
Previous stroke or transient ischemic attack	11	8
Left ventricular ejection fraction (%)	27±6	27±6
Primary classification of atrial fibrillation (%)		
Paroxysmal	33	30
Persistent¶	67	70
≥6 Mo since first diagnosis of atrial fibrillation (%)	41	46
Atrial fibrillation on electrocardiography (%)	54	61
QRS duration (msec)	112±30	115±30
Previous electrical cardioversion (%)	34	37
Left atrial dimension (mm)	49±7	49±7
Previous hospitalization (%)		
For atrial fibrillation	51	55
For congestive heart failure (during previous 6 mo)	54	56

Rhythm Control vs Rate Control for AF and HF
The AF-CHF Trial

Medical Therapy at 12 Months.*

Drug	Rhythm-Control Group (N = 682)	Rate-Control Group (N = 694)	P Value
	percent		
Amiodarone	82	7	<0.001
Sotalol	2	<1	0.02
Dofetilide	<1	<1	0.62
Beta-blocker	80	88	<0.001
Digoxin	51	75	<0.001
Verapamil or diltiazem	2	3	0.10
ACE inhibitor	81	82	0.41
ARB	16	13	0.09
ACE inhibitor or ARB	94	94	0.57
Diuretic	80	82	0.37
Aldosterone antagonist	47	49	0.51
Oral anticoagulant	88	92	0.03
Aspirin	34	31	0.33
Lipid-lowering drug	44	46	0.61

Rhythm Control vs Rate Control for AF and HF
The AF-CHF Trial
Sinus Rhythm Follow-up Visits

Roy D. AF-CHF Trial. N Engl J Med 2008; 358: 2667
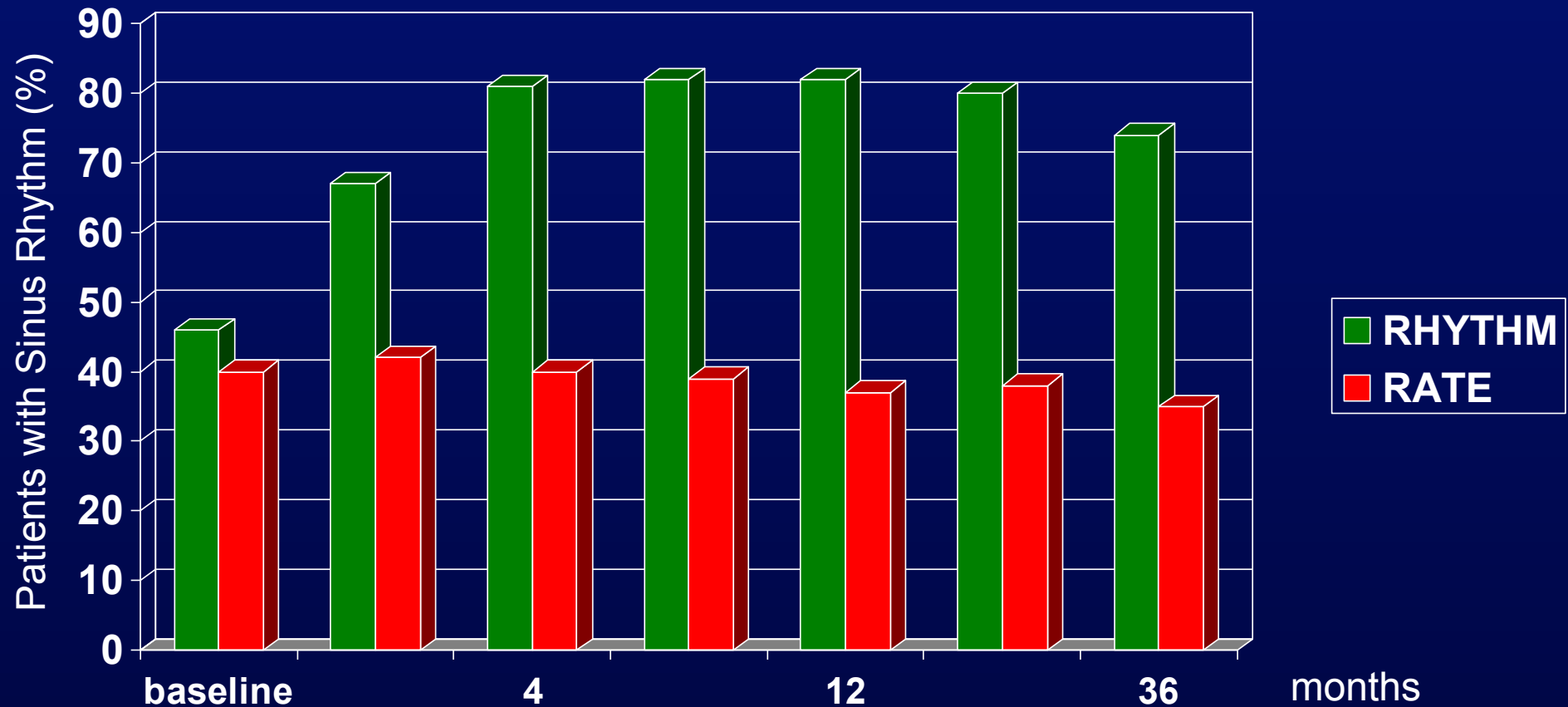
Atrial Fibrillation
Effect on Mortality of Rate vs Rhythm Control

Pts with Thromboembolic Risk Factors
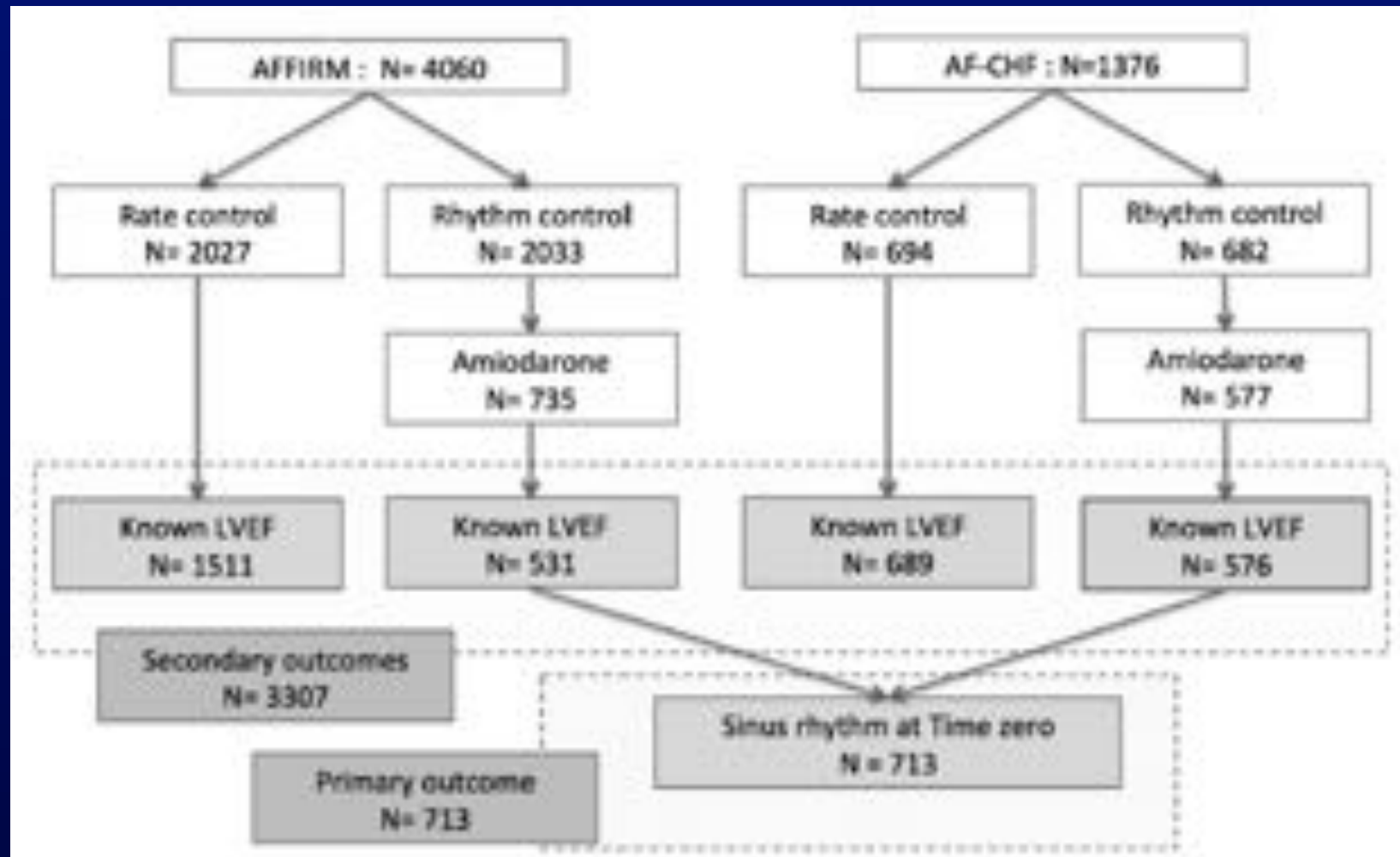
Pts with Heart Failure
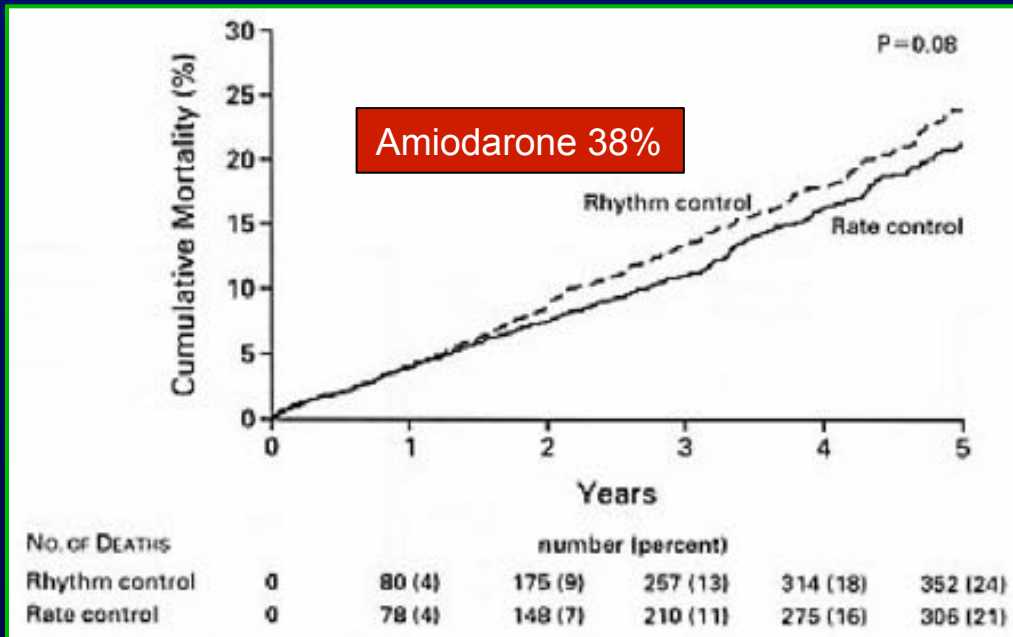
AFFIRM Trial
N Engl J Med 2002; 347: 1825
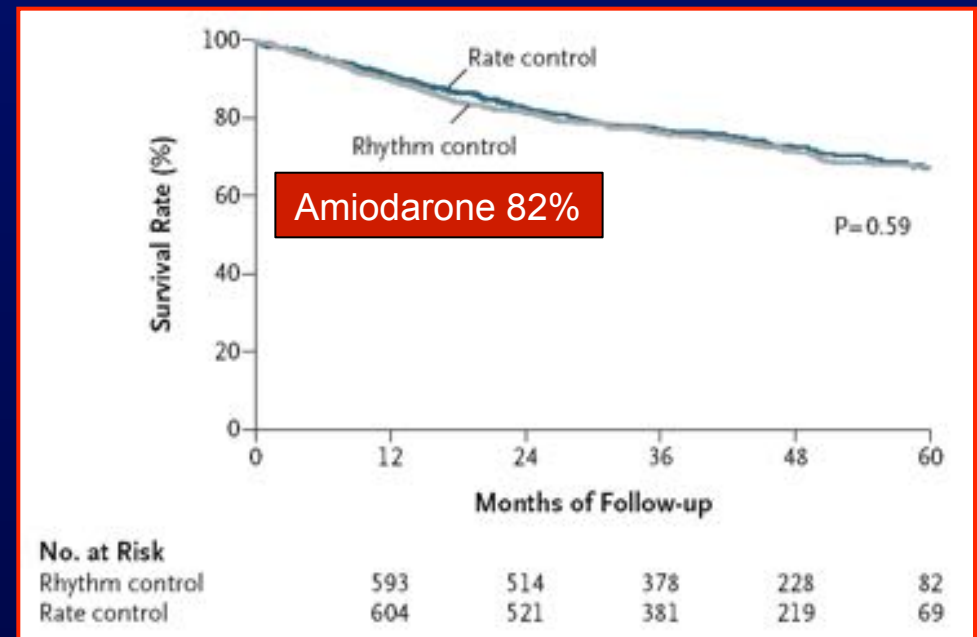
AF-CHF Trial
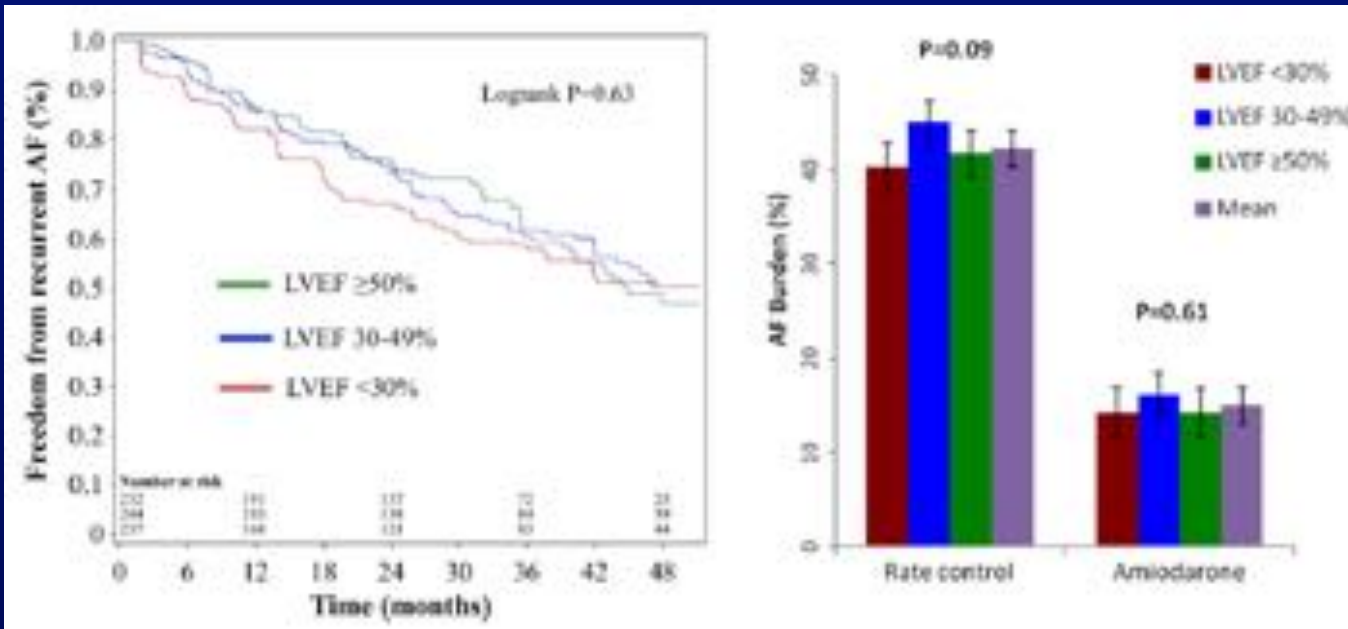N Engl J Med 2008; 358: 2667

Amiodarone in AF PTs with and w/out HF
Study Population from AFFIRM and AF-CHF Trials

Cadrin-Tourigny J. J Cardiovasc Electrophysiol 2014; 25: 1306-13

Amiodarone in AF PTs with and w/out HF

- 729 (22.0%) deaths occurred, 68.3% of which CV (N = 498; 15.1%)
- 450 (20.5%) deaths, 298 (13.5%) CV, in 2,200 pts ® to rate control
- 279 (25.2%) deaths, 200 (18.1%) CV, in 1,107 pts on amiodarone

Amiodarone in multivariate analyses
was NOT PREDICTIVE of overall mortality (p = 0.87)
or CV mortality (p = 0.90) in all pts, nor in those
with (HR 1.03, 95% CI [0.68–1.55], p = 0.8874) or
w/out (HR 1.02, 95% CI [0.63–1.65], p = 0.9328)
severe LV systolic dysfunction

Cadrin-Tourigny J. J Cardiovasc Electrophysiol 2014; 25: 1306-13

Amiodarone in Pts with LV Dysfunction
Conclusions

► Efficacy in maintaining SR and reducing the overall burden of AF was confirmed and was no different in pts with and w/out LV dysfunction

► Safety profile in the setting of left ventricular dysfunction can be confirmed

► No beneficial or harmful effects were observed with regards to mortality rates