

7° AP-HRS Scientific Session, New Dehli, India - Oct 29 to Nov 1, 2014

Antiarrhythmic agents in 2014

Antonio Raviele, MD, FESC, FHRS

President ALFA – Alliance to Fight Atrial fibrillation - Venice, Italy

Vaughan Williams Classification / AA Drugs



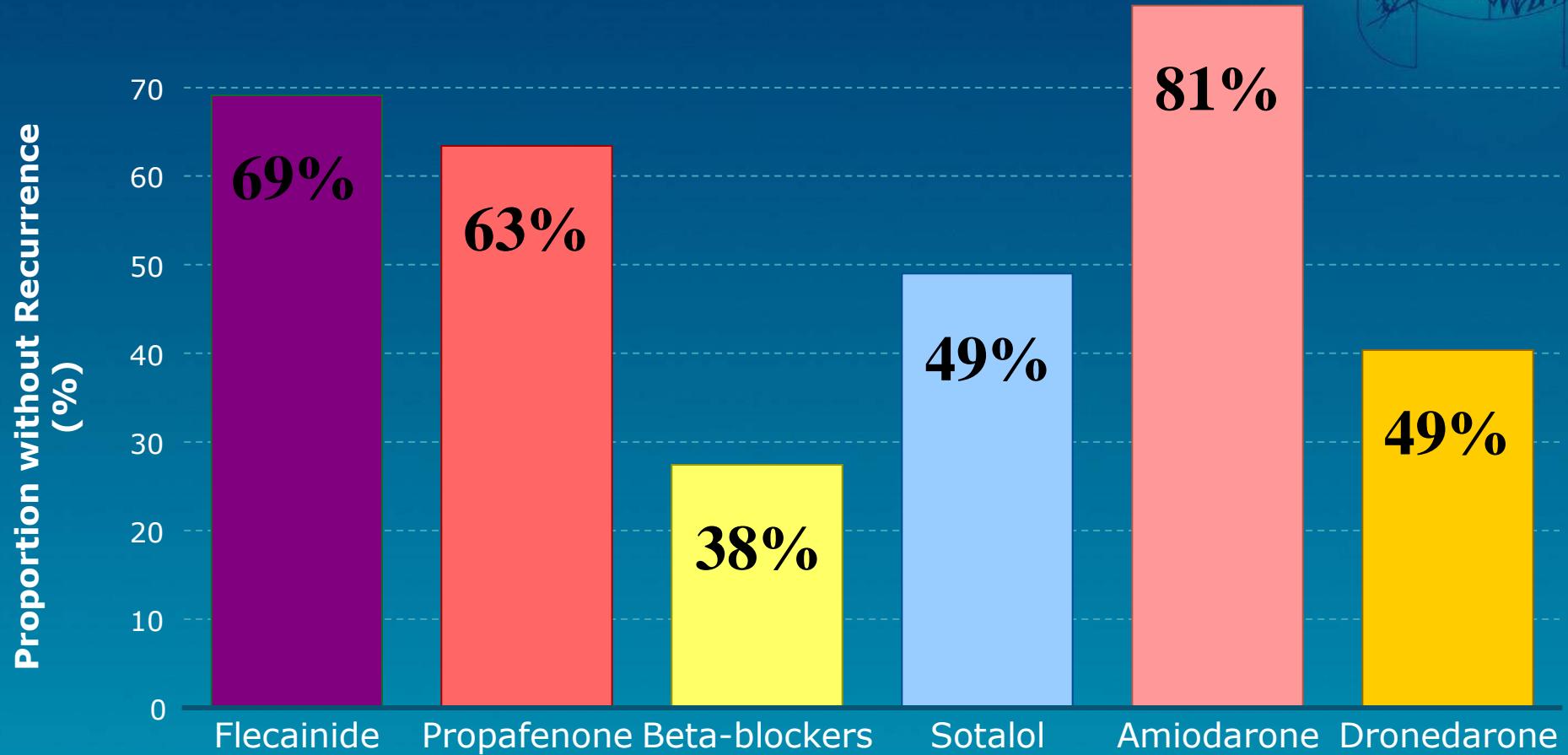
- Type IA
Disopyramide
Procainamide
Quinidine
- Type IB
Lidocaine
Mexiletine
- Type IC
Flecainide
Moricizine
Propafenone

- Type II
Beta-blockers
- Type III
Sotalol
Amiodarone
Dronedarone
Bretylium
Dofetilide
Ibutilide
- Type IV
Ca-antagonists

Suggested Doses for commonly used AADs

Drug	Dose
Flecainide	100-200 mg b.i.d.
Flecainide XL	200 mg o.d.
Propafenone	150-300 mg t.i.d.
Propafenone SR	225-425 mg b.i.d.
d,l-Sotalol	80-160 mg b.i.d.
Amiodarone	600 mg o.d. x 4 w. 400 mg o.d. x 4 w. then 200 mg o.d.
Dronedarone	400 mg b.i.d.

Reduction of the number of AF recurrences at 1 year FU in studies comparing AADs with placebo or no treatment



Pooled Recurrence Rates of AF at 1 year in patients treated with AADs



43% - 67%

Reduction of the number of AF recurrences at 1 year FU in studies comparing two AADs



Comparing two antiarrhythmics		Drug A	Drug B			
Disopyramide vs. Other Class I Drugs	2	26 / 60	27 / 53	0.76 (0.36 – 1.60)	-	ns
Quinidine vs. Flecainide	2	103 / 132	99 / 137	1.38 (0.79 – 2.41)	-	ns
Other Class I Drugs	4	176 / 258	168 / 268	1.30 (0.90 – 1.87)	-	ns
Sotalol	6	715 / 1109	556 / 869	0.92 (0.76 – 1.11)	-	ns
Flecainide vs. Propafenone	2	49 / 145	56 / 152	0.87 (0.54 – 1.40)	-	ns
Amiodarone vs. Class I Drugs	5	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 vs. 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



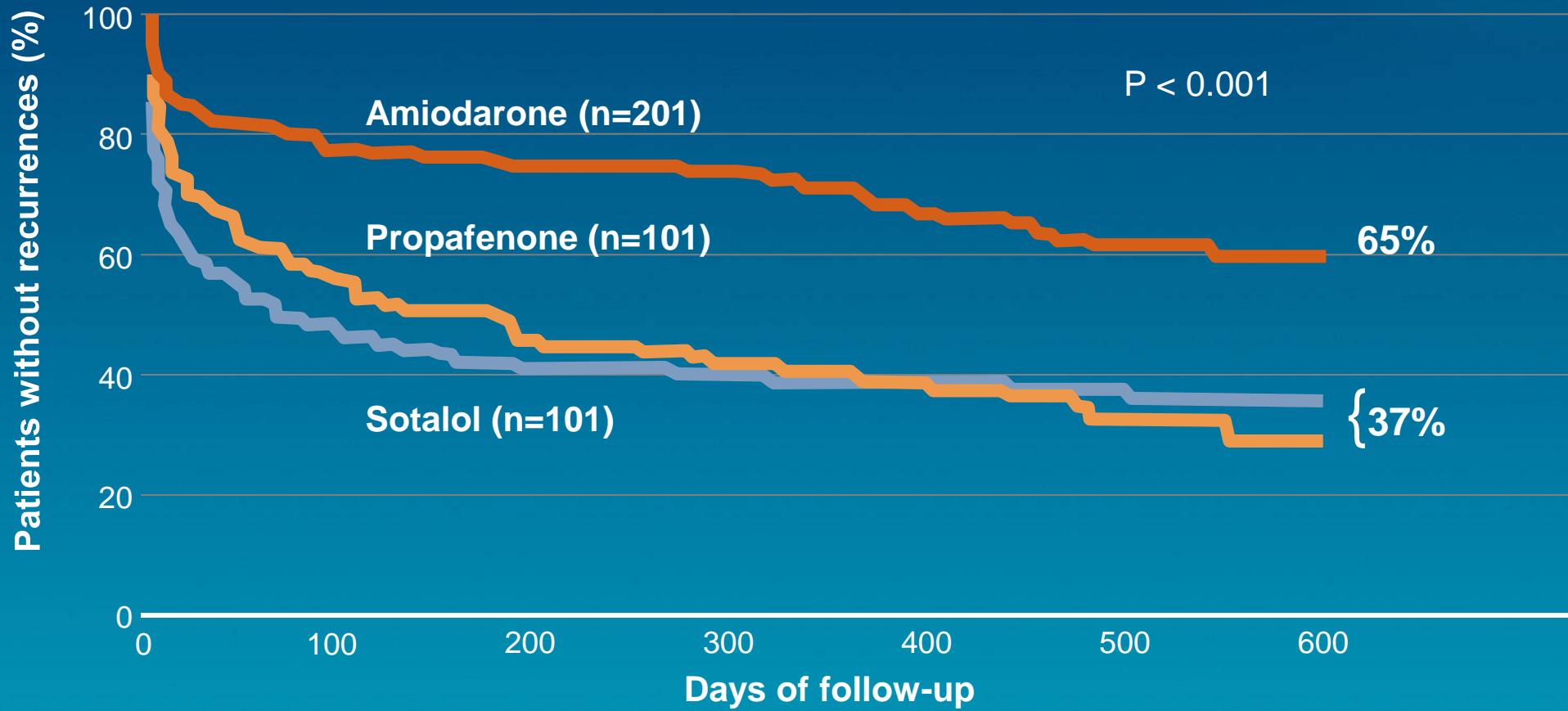
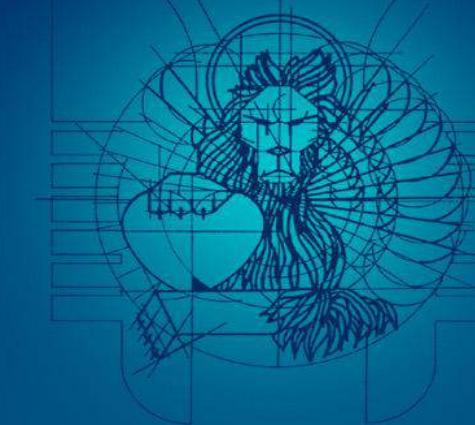
AMIODARONE TO PREVENT RECURRENCE OF ATRIAL FIBRILLATION

DENIS ROY, M.D., MARIO TALAJIC, M.D., PAUL DORIAN, M.D., STUART CONNOLLY, M.D.,
MARK J. EISENBERG, M.D., M.P.H., MARTIN GREEN, M.D., TERESA KUS, M.D., JEAN LAMBERT, PH.D.,
MARC DUBUC, M.D., PIERRE GAGNÉ, M.D., STANLEY NATTEL, M.D., AND BERNARD THIBAULT, M.D.,
FOR THE CANADIAN TRIAL OF ATRIAL FIBRILLATION INVESTIGATORS*

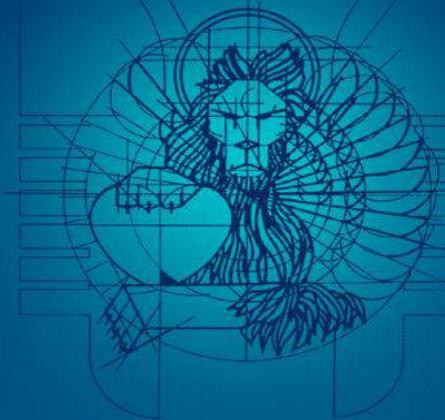
N Engl J Med 2000;342:913-20

Canadian Trial of AF (CTAF)

Mean Follow-up: 16 months



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



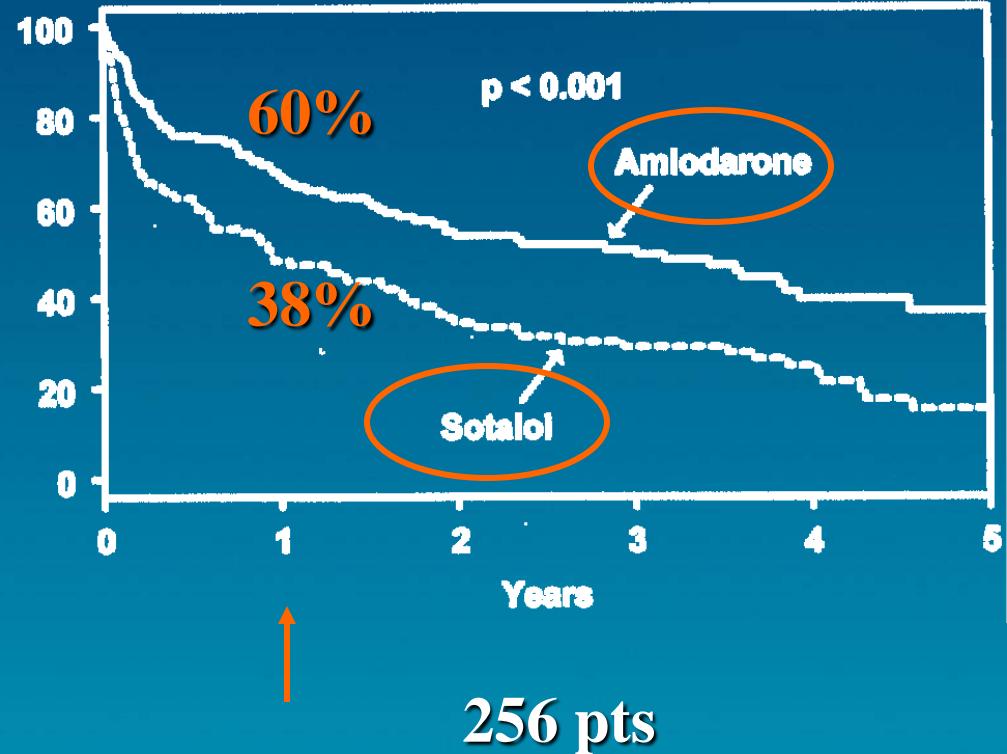
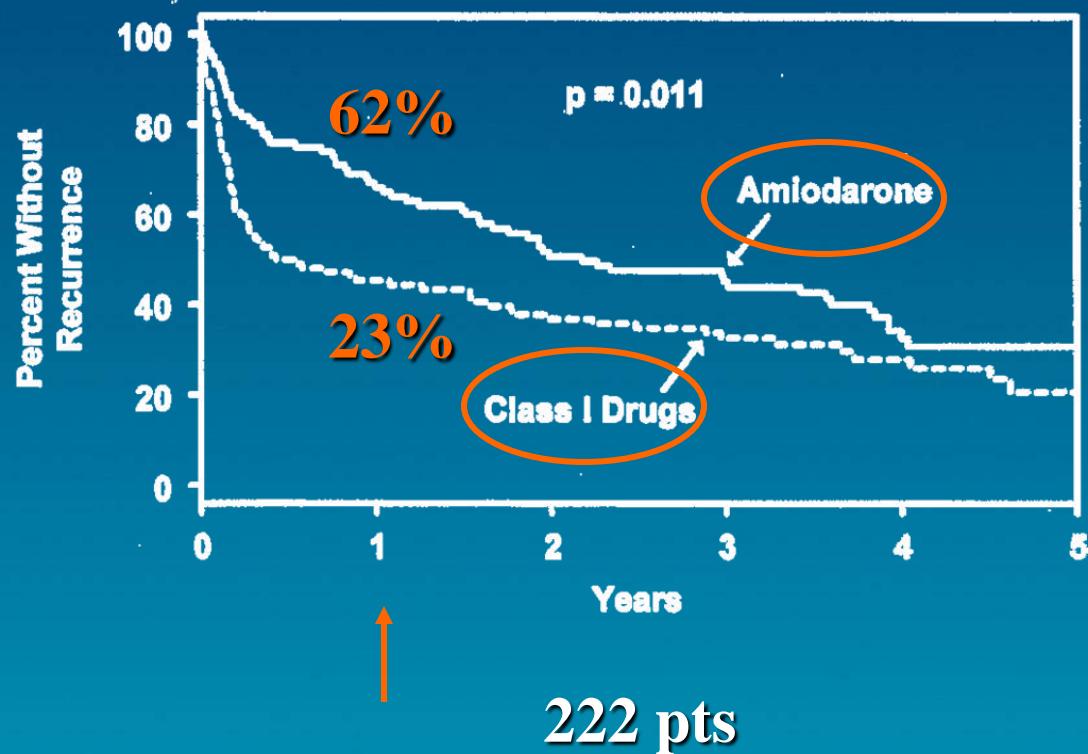
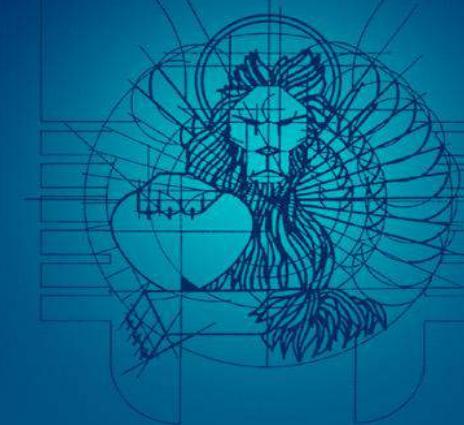
Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

An AFFIRM Substudy of the First Antiarrhythmic Drug

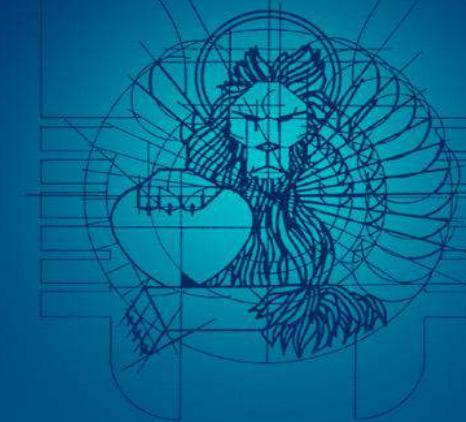
The AFFIRM First Antiarrhythmic Drug Substudy Investigators

J Am Coll Cardiol 2003; 42: 20-9

AFFIRM Substudy of the first Antiarrhythmic Drug



(AFFIRM Investigators. JACC 2003; 42: 20-9)



Amiodarone versus Sotalol for Atrial Fibrillation

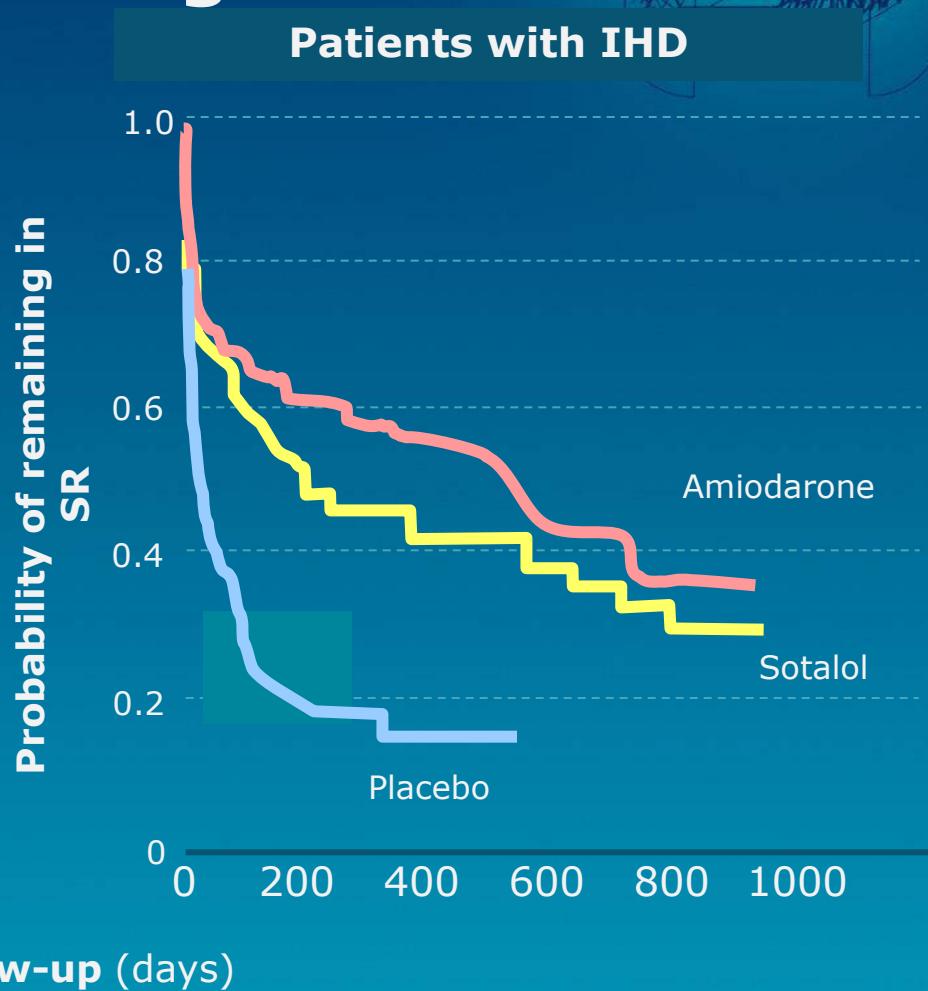
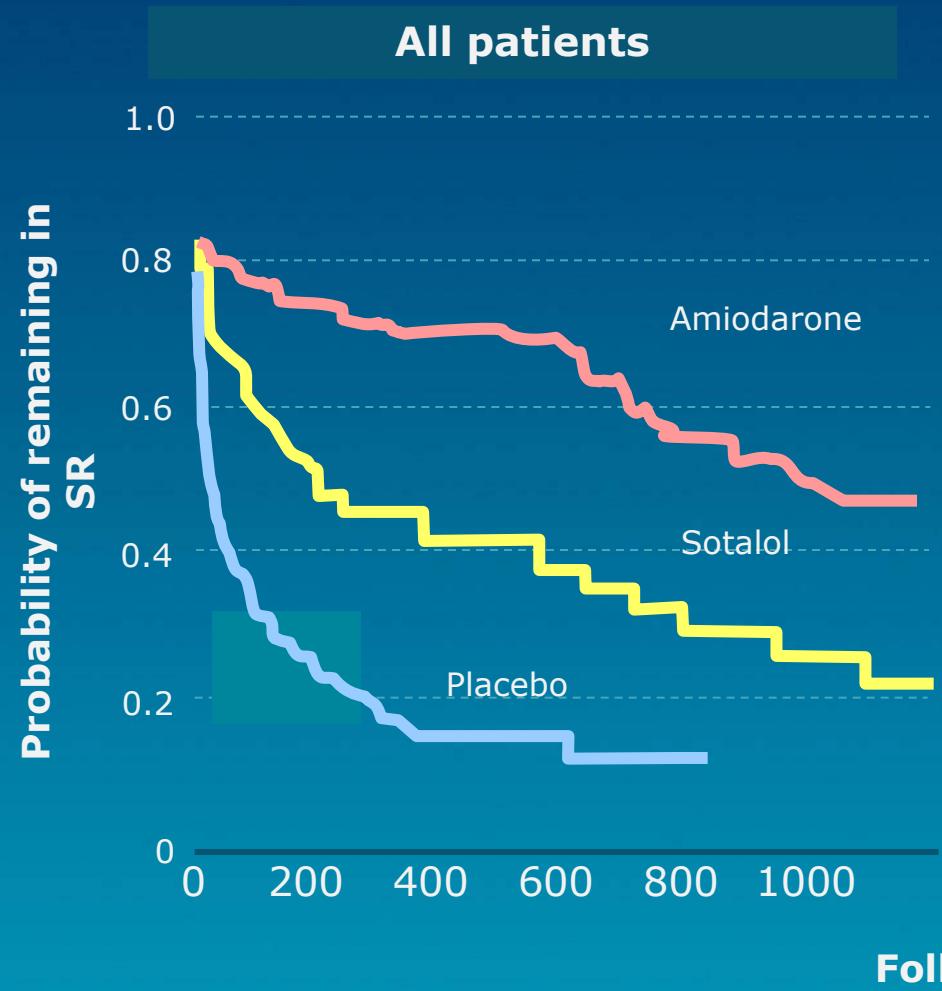
Bramah N. Singh, M.D., D.Sc., Steven N. Singh, M.D., Domenic J. Reda, Ph.D., X. Charlene Tang, M.D., Ph.D., Becky Lopez, R.N., Crystal L. Harris, Pharm.D., Ross D. Fletcher, M.D., Satish C. Sharma, M.D., J. Edwin Atwood, M.D., Alan K. Jacobson, M.D., H. Daniel Lewis, M.D., Dennis W. Raisch, Ph.D., Michael D. Ezekowitz, M.B., Ch.B., Ph.D. and the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators

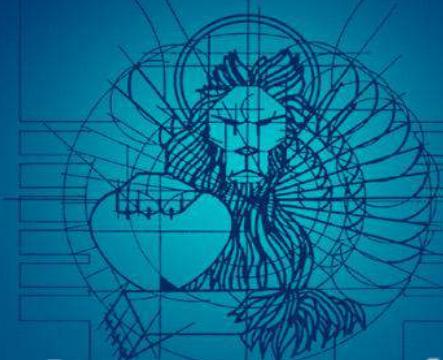
N Engl J Med 2005; 352: 1861-1872

Amiodarone and Sotalol Equivalent in Patients with Ischaemic Heart Disease



SAFE-T Investigators

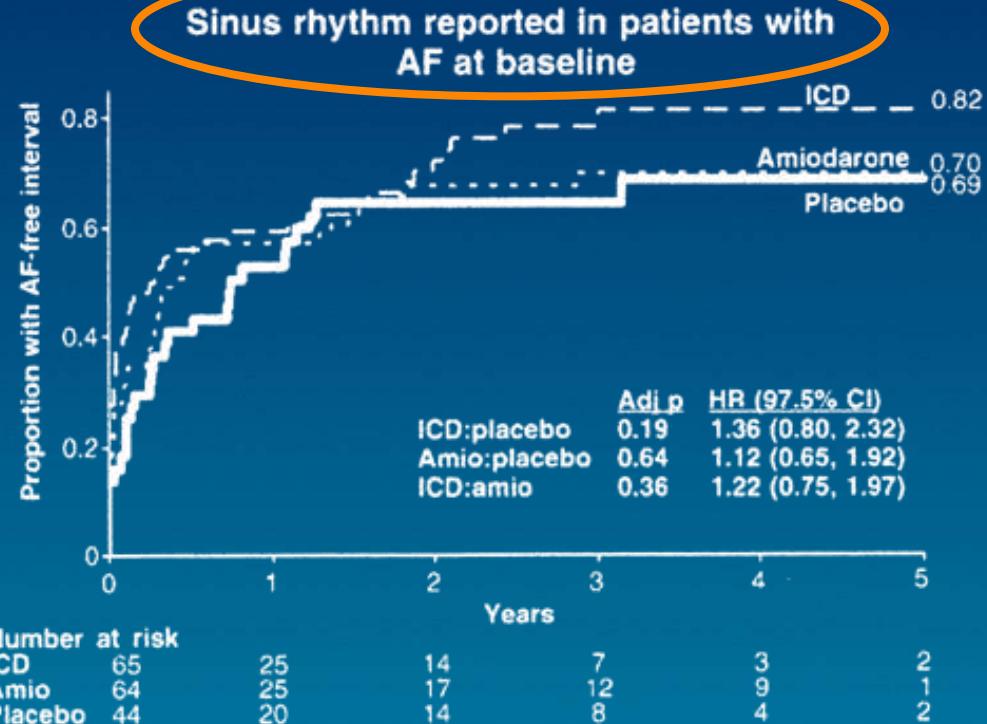




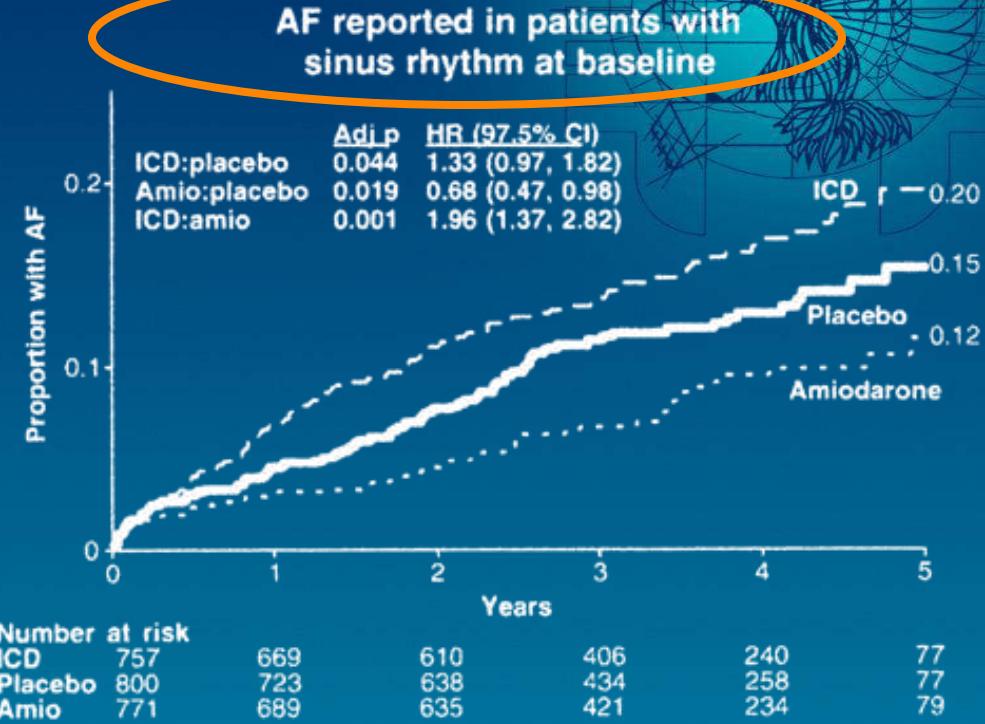
Role of amiodarone or implantable cardioverter/defibrillator in patients with atrial fibrillation and heart failure

Steven N. Singh, MD,^a Jeannie Poole, MD,^b Jill Anderson, RN,^b Anne S. Hellkamp, PhD,^c Pamela Karasik, MD,^a Daniel B. Mark, MD,^c Kerry L. Lee, PhD,^c and Gust H. Bardy, MD^b
for the SCD-HeFT Investigators *Washington, DC; Seattle, WA; and Durham, NC*

Am Heart J 2006; 152: 974.e7–974.e11



Kaplan-Meier curves for incidence of AF in patients with SR at baseline and according to assigned therapy.



Kaplan-Meier curves for incidence of SR in patients with AF at baseline and according to assigned therapy.



AMIODARONE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND ASYMPTOMATIC VENTRICULAR ARRHYTHMIA

STEVEN N. SINGH, M.D., ROSS D. FLETCHER, M.D., SUSAN GROSS FISHER, PH.D., BRAMAH N. SINGH, M.D., H. DANIEL LEWIS, M.D., PRAKASH C. DEEDWANIA, M.D., BARRY M. MASSIE, M.D., CINDY COLLING, R.PT., AND DIANE LAZZERI, M.I.A., FOR THE SURVIVAL TRIAL OF ANTIARRHYTHMIC THERAPY IN CONGESTIVE HEART FAILURE*

N Engl J Med 1995; 333: 77-82

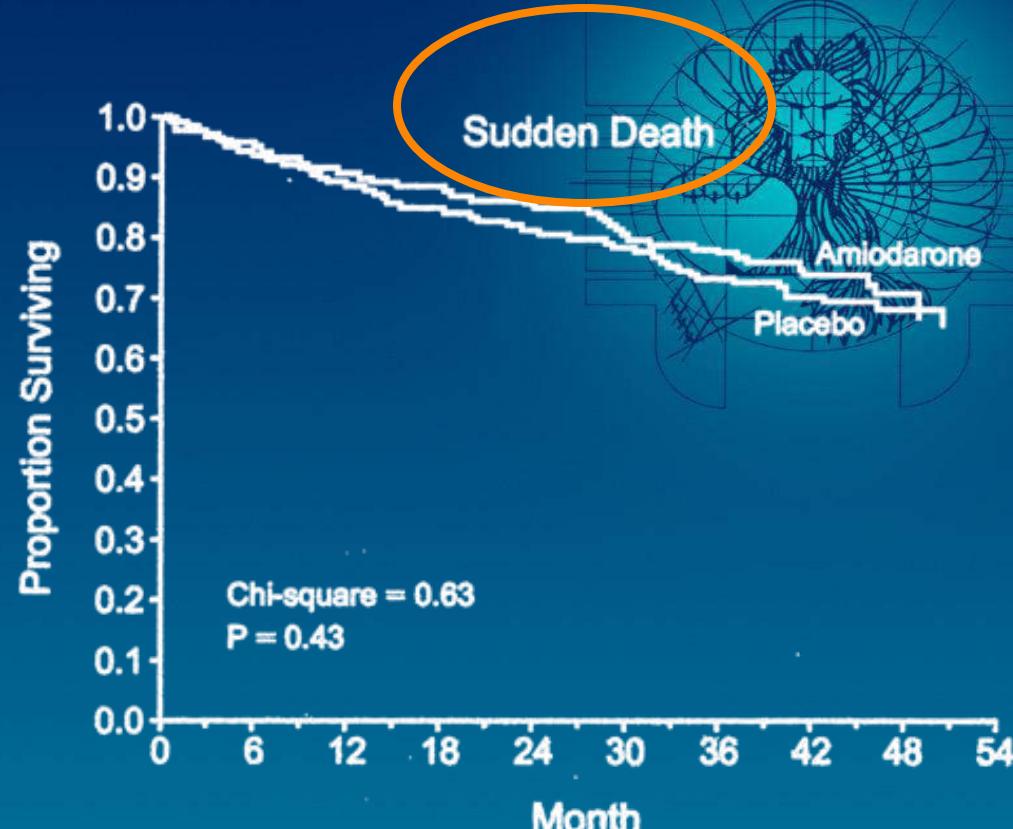
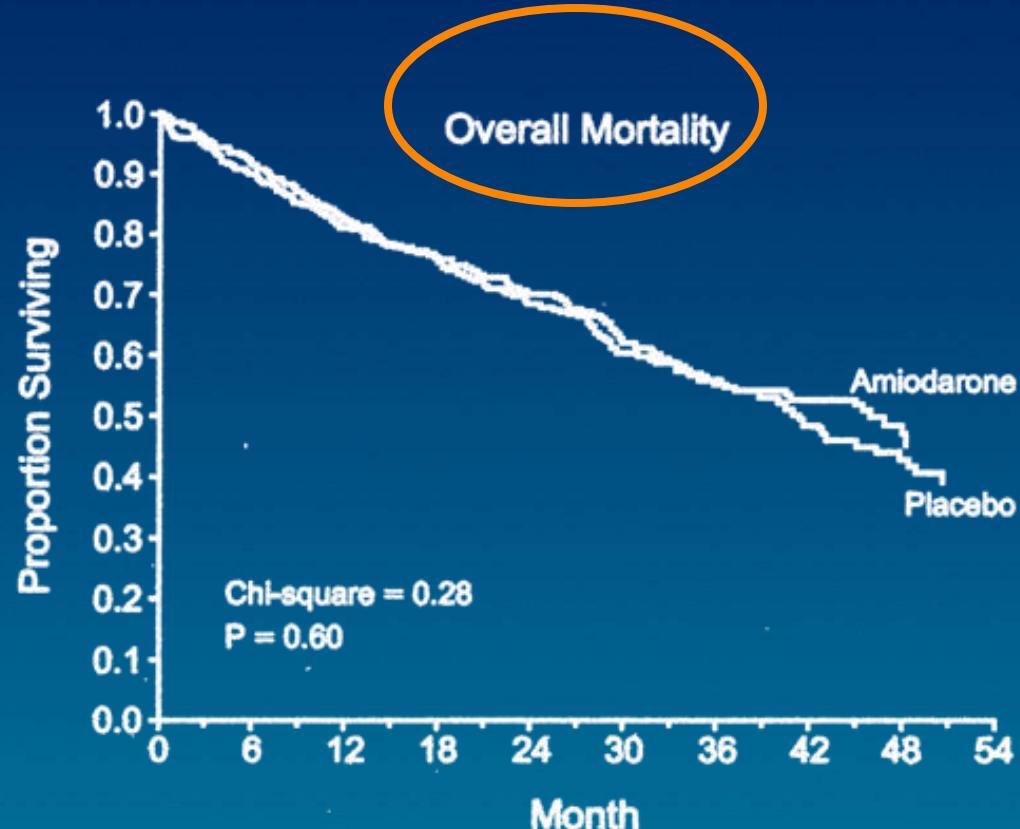


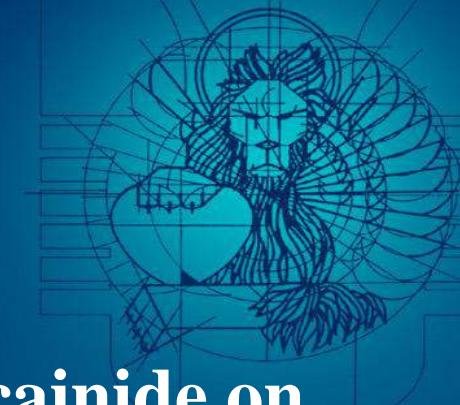
Figure 1. Kaplan-Meier Estimates of Overall Mortality and Sudden Death from Cardiac Causes.

Amiodarone had no significant effect, as compared with placebo, on either overall mortality or the incidence of sudden death. The numbers below the figures are the numbers of patients at risk.

AADs in HF patients



- With the only exception of Amiodarone, **all the other AADs have a negative inotropic effect** that can induce or worsen congestive HF and increase mortality

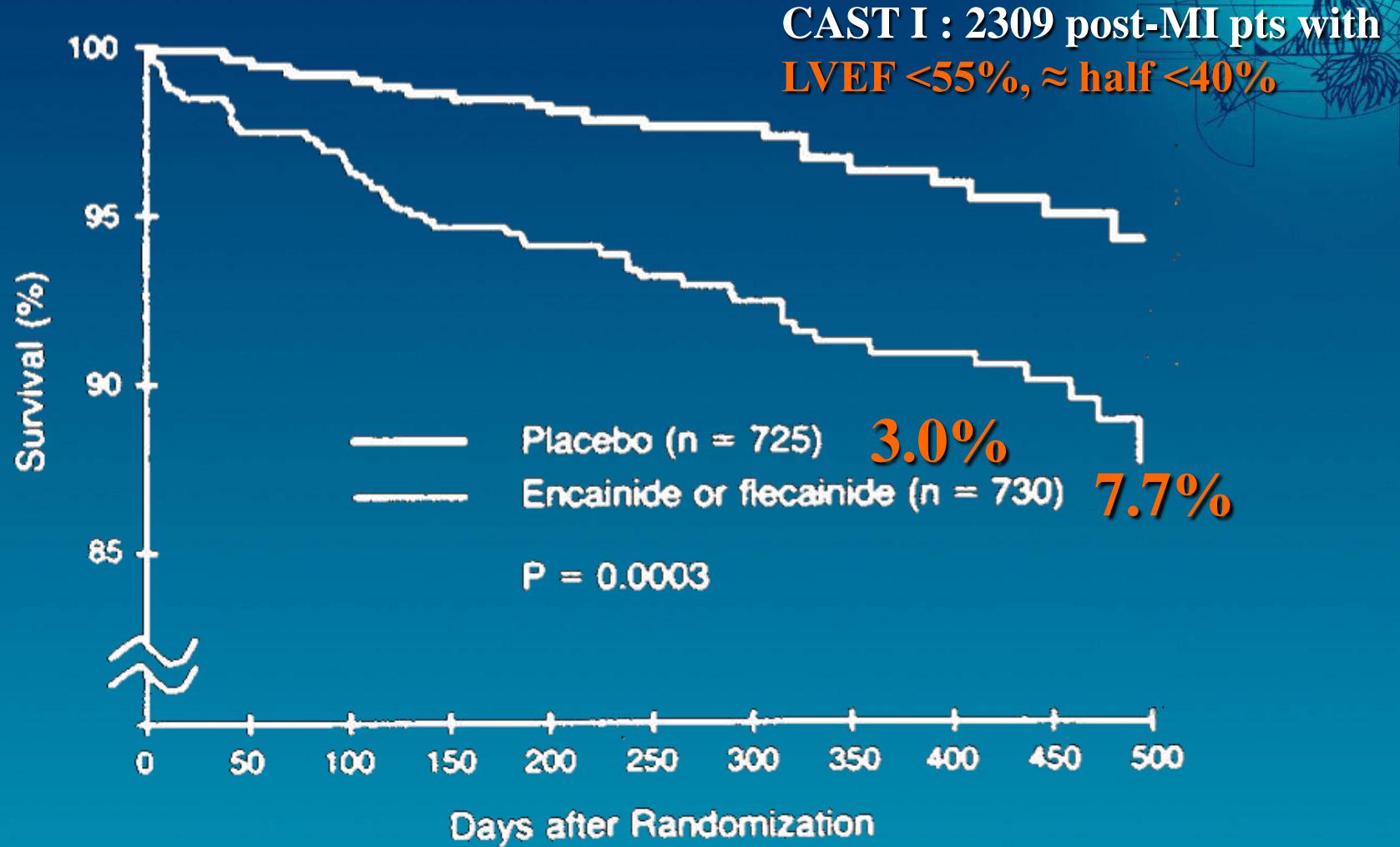


Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction

The Cardiac Arrhythmia Suppression Trial (CAST) Investigators.

N Engl J Med 1989; 321: 406-412

Effects of flecainide on all-cause mortality in post-MI



CAST I N Engl J Med 1989; 321: 406-12

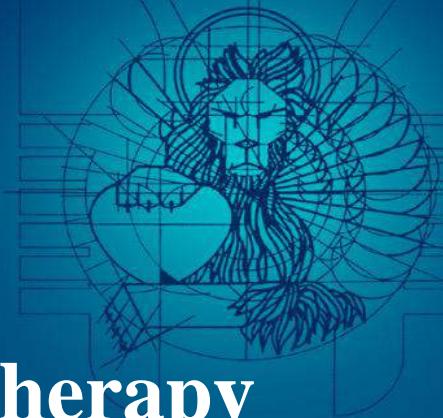
Adverse Events of the 3 Treatment Assignments.

Table 4. Adverse Events of the 3 Treatment Assignments

Optic Trial

Adverse Event	No. of Patients (%)			P Value*
	β-Blocker (n = 138)	Amiodarone + β-Blocker (n = 140)	Sotalol (n = 134)	
Death	2 (1.4)	6 (4.3)	4 (3.0)	.36
Arrhythmic death	1 (0.7)	2 (1.4)	1 (0.8)	.60
Myocardial infarction	1 (0.7)	1 (0.7)	0	.62
Heart failure	9 (6.5)	12 (8.6)	14 (13.4)	.14
Atrial fibrillation	6 (4.4)	1 (0.7)	6 (4.5)	.13
Pulmonary adverse event	0	7 (5.0)	4 (3.0)	.03
Hypothyroidism	0	6 (4.3)	1 (0.8)	.01
Hyperthyroidism	0	2 (1.4)	0	.14
Symptomatic bradycardia	1 (0.7)	8 (6.4)	2 (1.5)	.009
Torsades de pointes	0	0	0	>.99
Skin adverse event	2 (1.5)	4 (2.9)	3 (2.2)	.72
Device infection	1 (0.7)	2 (1.4)	4 (3.0)	.34
Hospitalized during follow-up	60 (43.3)	49 (34.9)	40 (30.1)	.32

*For any difference between 3 treatment assignments.



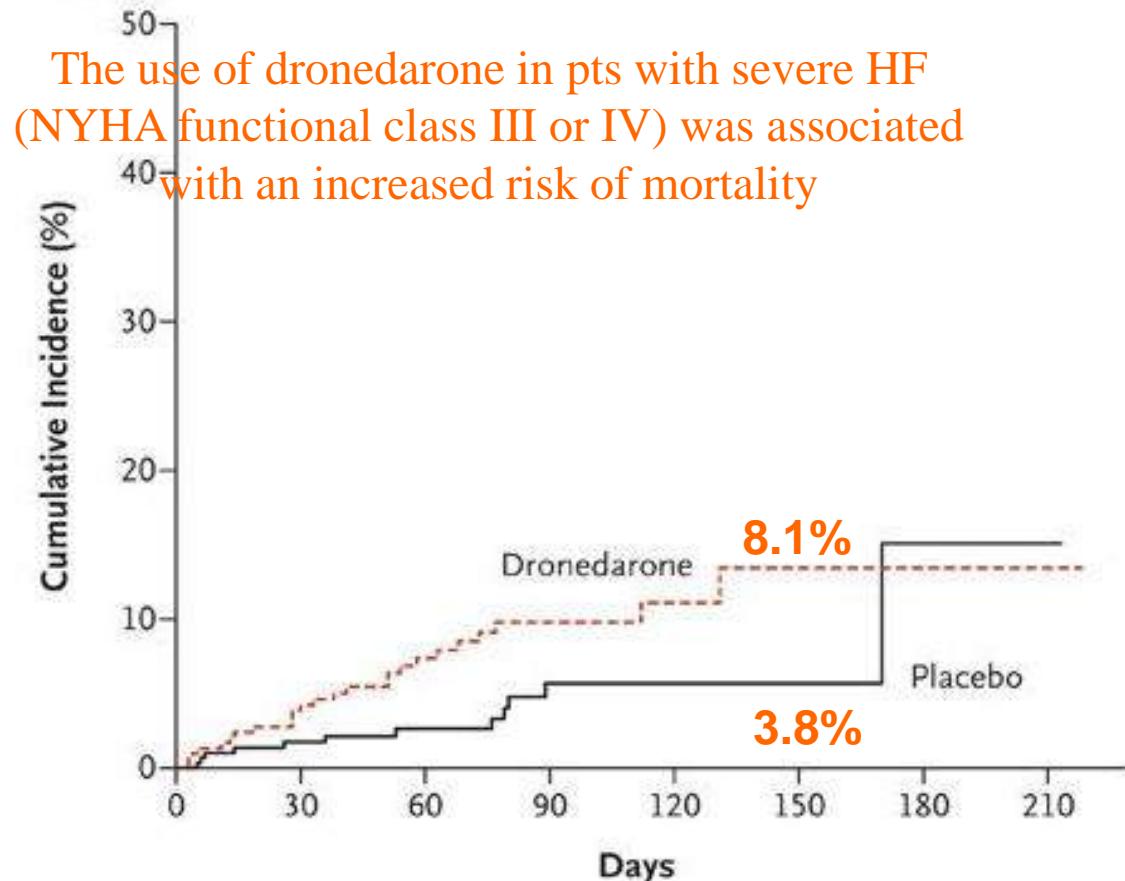
Increased Mortality after Dronedarone Therapy for Severe Heart Failure

Lars Køber, M.D., Christian Torp-Pedersen, M.D., John J.V. McMurray, M.D., Ole Gøtzsche, M.D., Samuel Lévy, M.D., Harry Crijns, M.D., Jan Amlie, M.D., Jan Carlsen, M.D., for the Dronedarone Study Group (**Andromeda Study**)

N Engl J Med 2008; 358: 2678-2687

All-cause mortality

B All-Cause Mortality



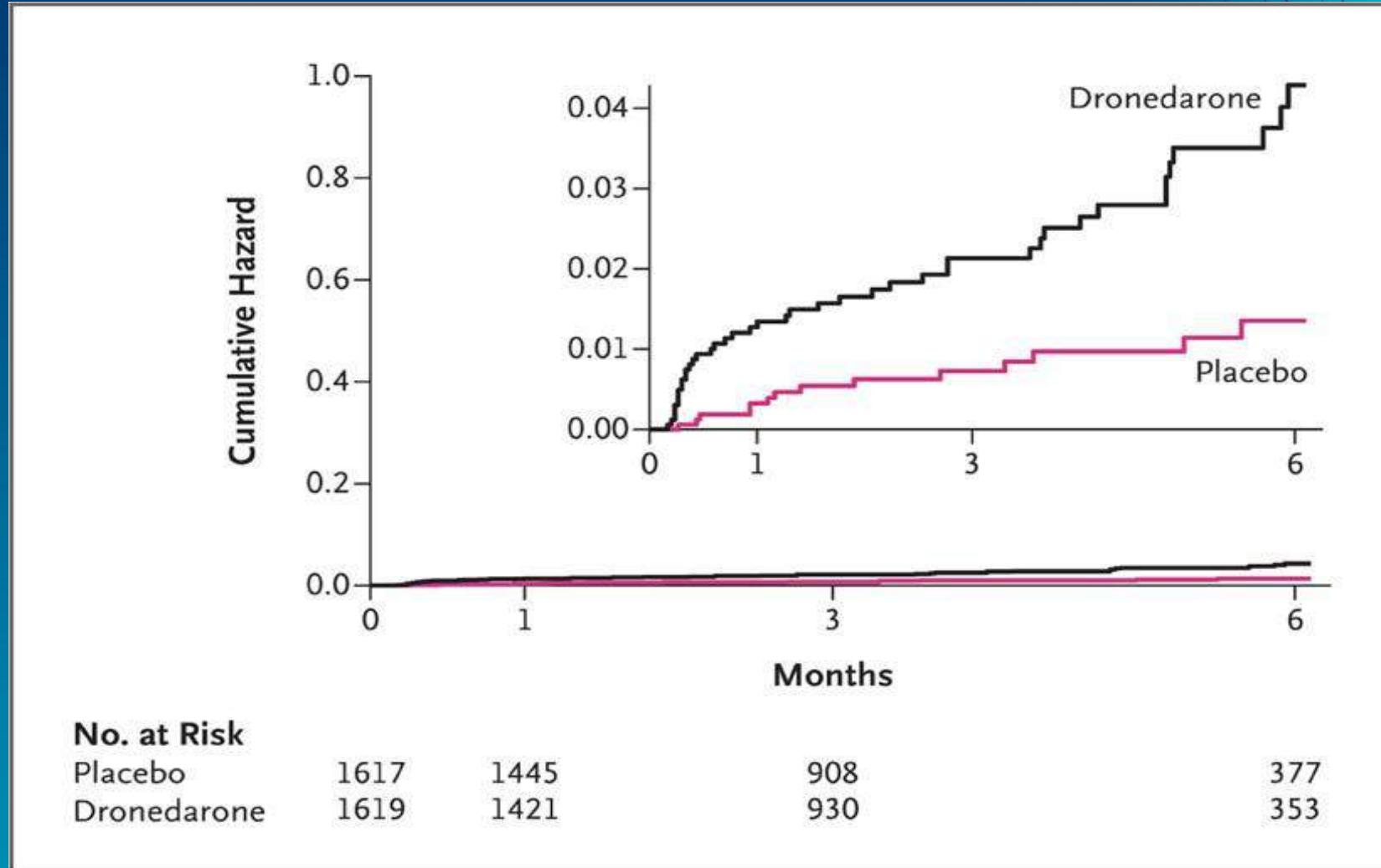
No. at Risk

Placebo	317	256	181	103	50	18	6	1
Dronedarone	310	257	174	104	59	22	5	1

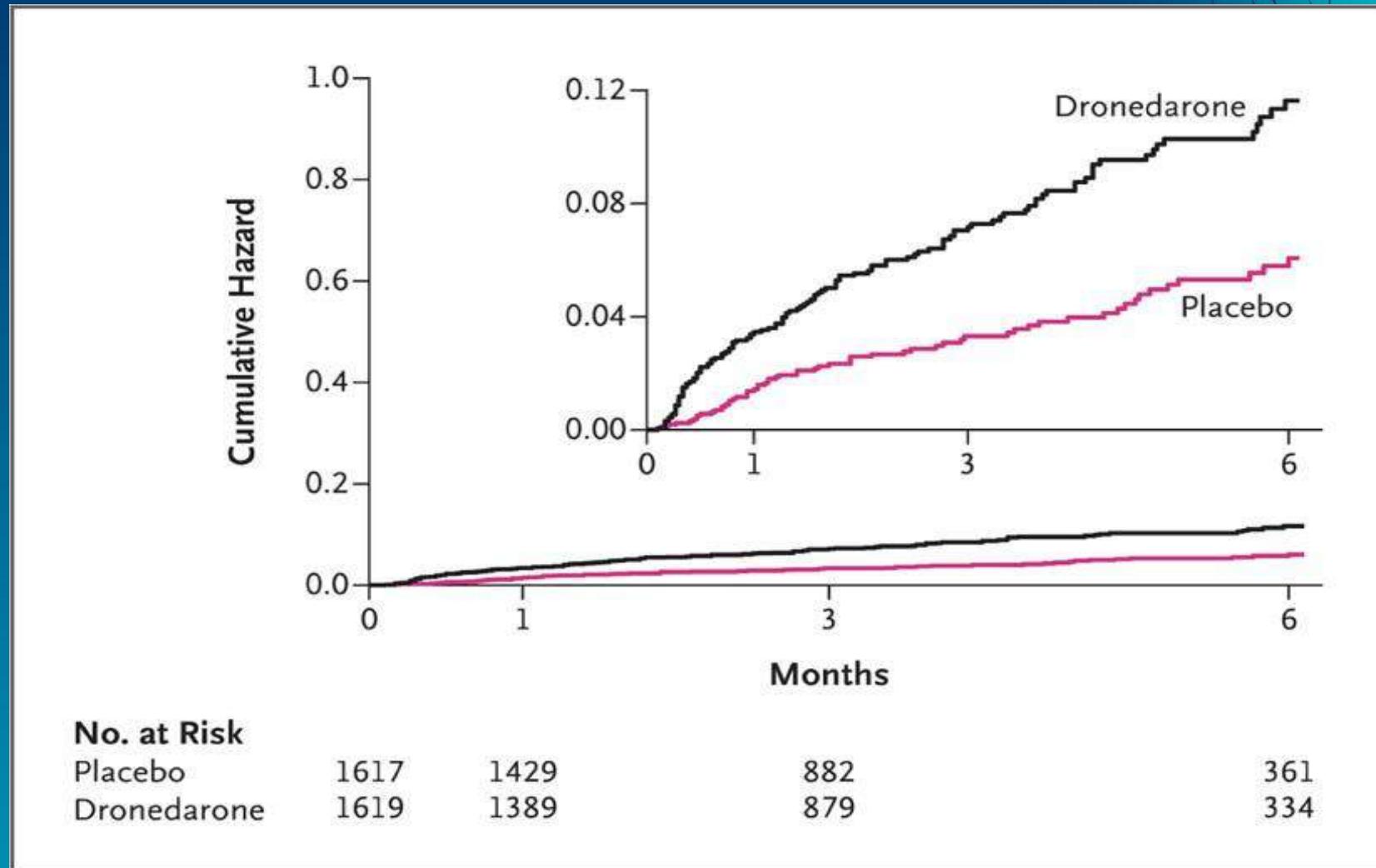
Dronedarone in High-Risk Permanent Atrial Fibrillation

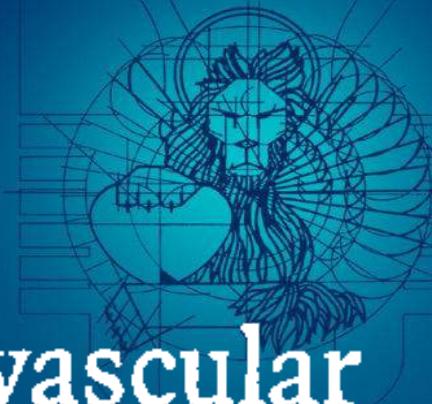
Stuart J. Connolly, M.D., A. John Camm, M.D., Jonathan L. Halperin, M.D.,
Campbell Joyner, M.D., Marco Alings, M.D., John Amerena, M.D., Dan Atar, M.D.,
Álvaro Avezum, M.D., Per Blomström, M.D., Martin Borggrefe, M.D.,
Andrzej Budaj, M.D., Shih-Ann Chen, M.D., Chi Keong Ching, M.D.,
Patrick Commerford, M.D., Antonio Dans, M.D., Jean-Marc Davy, M.D.,
Etienne Delacrétaz, M.D., Giuseppe Di Pasquale, M.D., Rafael Diaz, M.D.,
Paul Dorian, M.D., Greg Flaker, M.D., Sergey Golitsyn, M.D.,
Antonio Gonzalez-Hermosillo, M.D., Christopher B. Granger, M.D.,
Hein Heidbüchel, M.D., Josef Kautzner, M.D., June Soo Kim, M.D.,
Fernando Lanas, M.D., Basil S. Lewis, M.D., Jose L. Merino, M.D.,
Carlos Morillo, M.D., Jan Murin, M.D., Calambur Narasimhan, M.D.,
Ernesto Paolasso, M.D., Alexander Parkhomenko, M.D., Nicholas S. Peters, M.D.,
Kui-Hian Sim, M.D., Martin K. Stiles, M.D., Supachai Tanomsup, M.D.,
Lauri Toivonen, M.D., János Tomcsányi, M.D., Christian Torp-Pedersen, M.D.,
Hung-Fat Tse, M.D., Panos Vardas, M.D., Dragos Vinereanu, M.D.,
Denis Xavier, M.D., Jun Zhu, M.D., Jun-Ren Zhu, M.D., Lydie Baret-Cormel, M.D.,
Estelle Weinling, Pharm.D., Christoph Staiger, M.D., Salim Yusuf, M.D.,
Susan Chrolavicius, R.N., B.A., Rizwan Afzal, M.Sc., and Stefan H. Hohnloser, M.D.,
for the PALLAS Investigators*

Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).



Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).



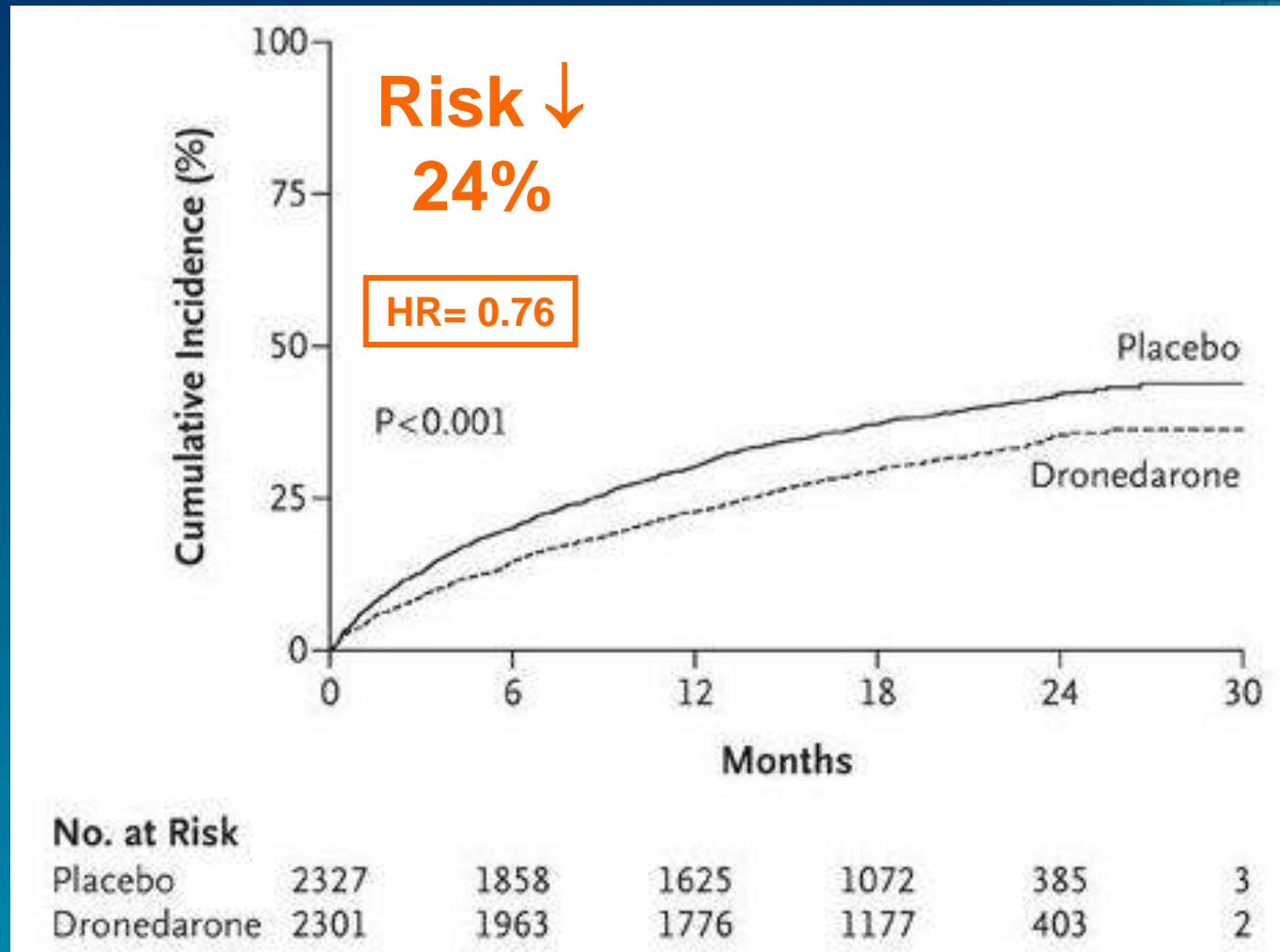


Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D.,
Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D.,
and Stuart J. Connolly, M.D., for the ATHENA Investigators*

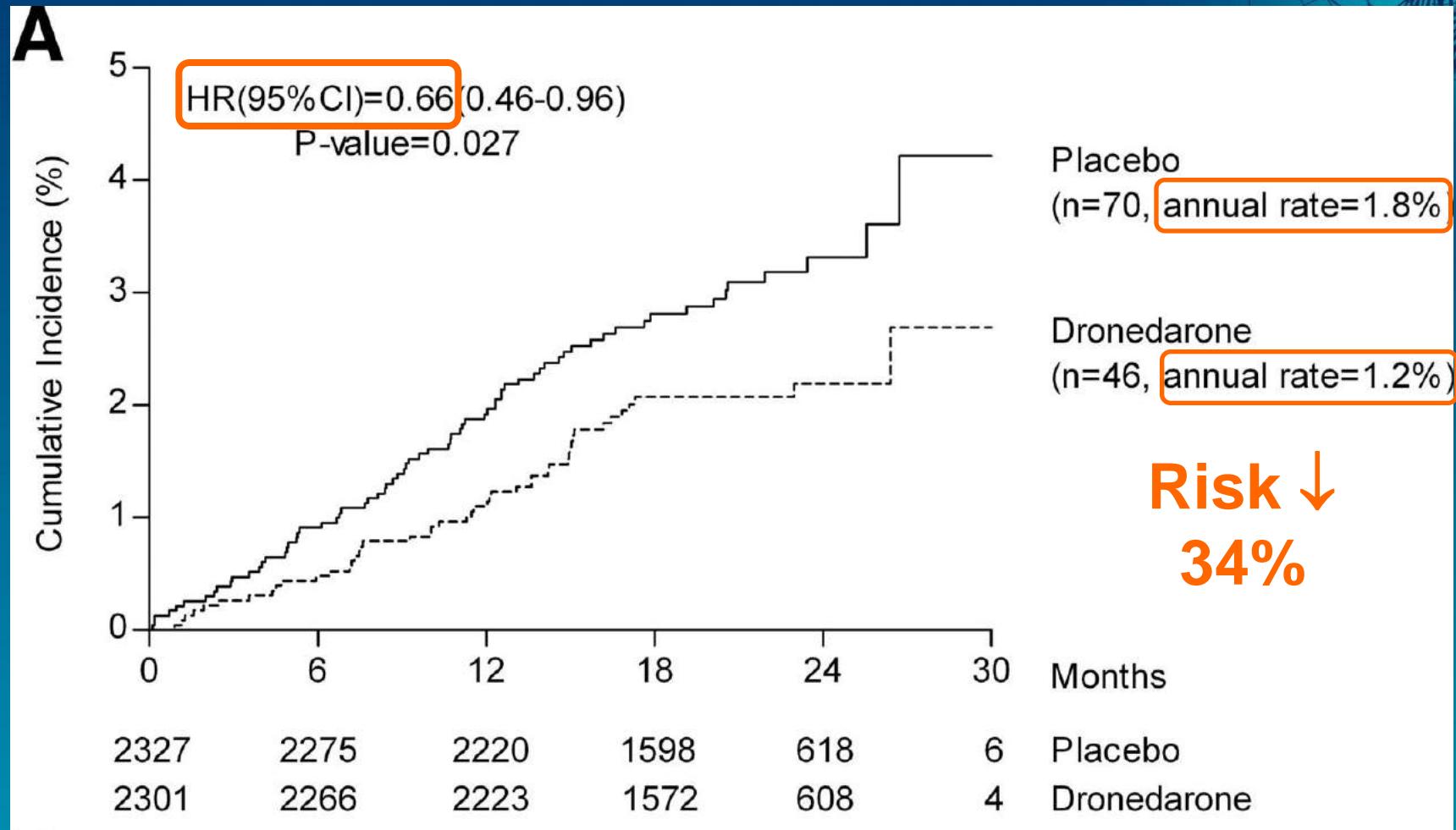
N Engl J Med 2009; 360: 668-78

Time to First Cardiovascular Hospitalization or Death



Dronedarone significantly reduced the incidence of the primary end-point by 24%

Cumulative risk of stroke (A)



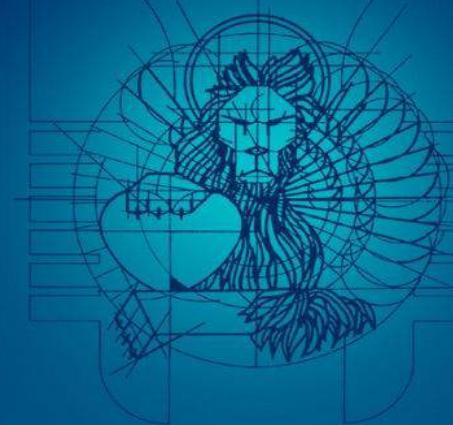
ATHENA (Overall) vs PALLAS Risk Factors

PALLAS Risk Factors	ATHENA (Overall)		PALLAS	
	Dronedarone n = 2301 %	Placebo n = 2327 %	Dronedarone (n = 1619) %	Placebo (n = 1617) %
CAD	28.7	31.3	40.9	41.2
Prior Stroke/TIA	7.3	7.1	26.9	28.3
Symptomatic HF	-	-	14.4	14.8
LVEF \leq 40%	4.2	4.7	21.3	20.7
Peripheral Arterial Disease	-	-	11.6	13.2
Age \geq 75 with HTN & Diabetes	2.1	2.7	18.2	17.1

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

Connolly S, et al. N Engl J Med 2011 Dec 15;365(24):2268-76

AADs for AF prevention



- It is indisputably true that amiodarone is the most potent AAD for the prevention of AF

Amiodarone / Potential adverse effects

✓ cardiac	torsade de pointe bradycardia	< 1% 5%
✓ hypothyroidism		6%
✓ hyperthyroidism		0.9%-2%
✓ pulmonary toxicity		1%-17%
✓ hepatotoxicity	↑ enzyme levels hepatitis/cyrosis	15%-30% < 3%
✓ corneal microdeposits		>90%
✓ optic neuropathy/neuritis		≤1%-2%
✓ blue-gray skin discoloration		4%-9%
✓ photosensitivity		25%-75%
✓ tremor/ataxia		3%-35%
✓ peripheral neuropathy		0.3% yr



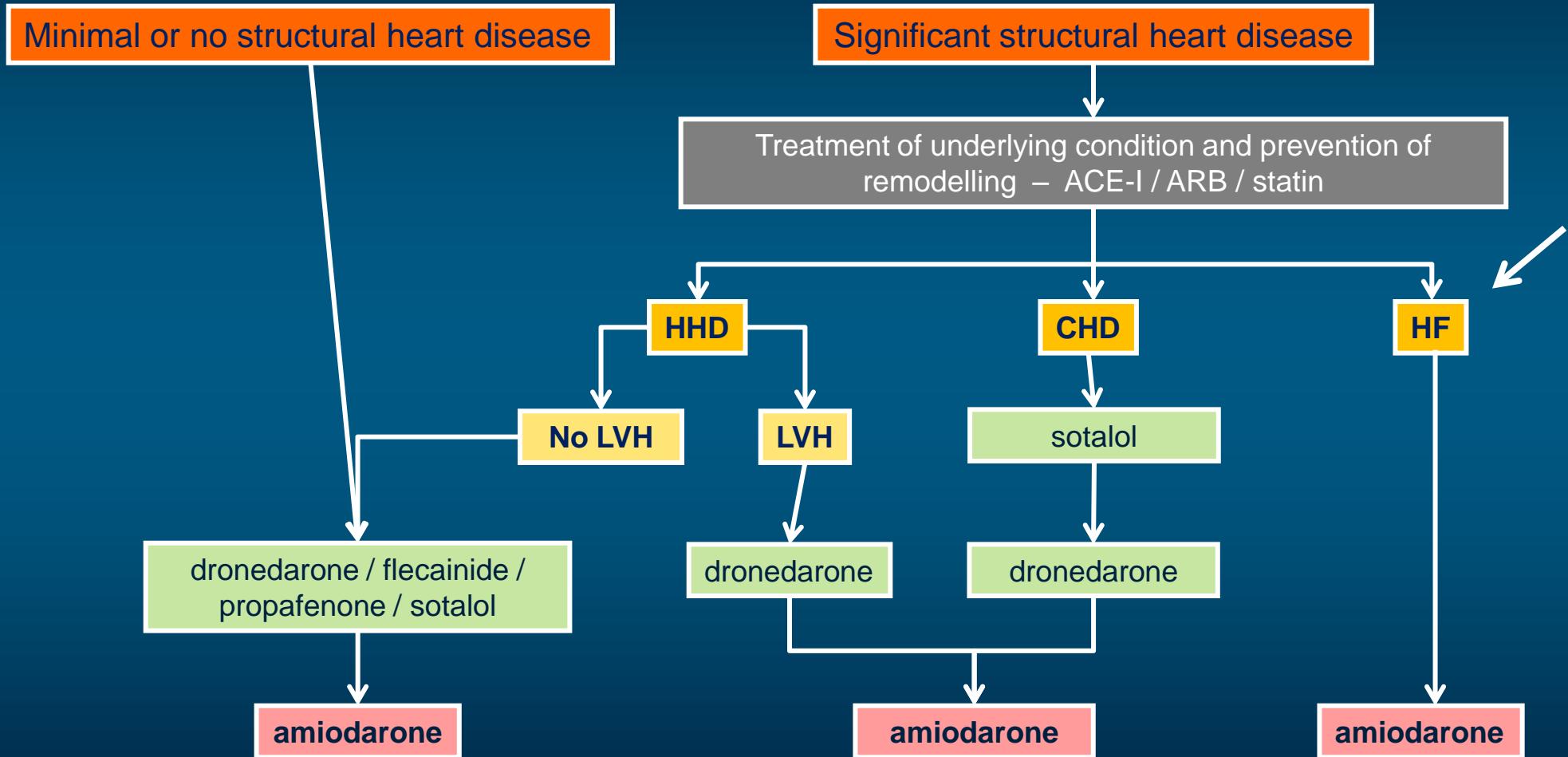
Choice of an antiarrhythmic drug for AF control

Recommendations	Class ^a	Level ^b
The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease: <ul style="list-style-type: none">• amiodarone• dronedarone• flecainide• propafenone• d,l-sotalol	I	A
Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy) or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C).	I	A C
In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.	I	B

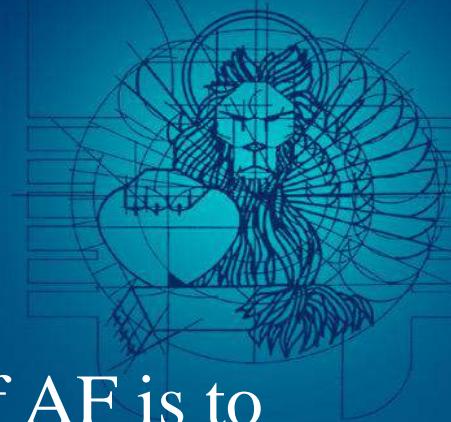
^aClass of recommendation. ^bLevel of evidence.

AF = atrial fibrillation; AV = atrioventricular; LoE = level of evidence; NYHA = New York Heart Association.

Choice of Oral Antiarrhythmic Drug



Conclusions (1)



- The rationale for pharmacological treatment of AF is to improve quality of life by reducing AF-related symptoms
- Efficacy of AADs to maintain sinus rhythm is modest
- Clinically successful AAD therapy may reduce rather than eliminate recurrence of AF
- If one AAD fails a clinically acceptable response may be achieved with another agent

Conclusions (2)



- Safety rather efficacy considerations should primarily guide the choice of antiarrhythmic agent
- Selection of the most appropriate AADs in the single patient should be based on a strict respect of current indications and contraindications
- Drug-induced proarrhythmia or extra-cardiac side effects are frequent

Conclusions (3)

- Adequate patient and physician education and awareness of the side effects of AADs is highly desirable
- Drug titration with incremental increase of dosage to a level that provides the desired effect should be systematically performed to test drug tolerance
- Evaluation of potential interactions with other drugs, especially in elderly people and patients with comorbidities is raccomandable





Novel AADs

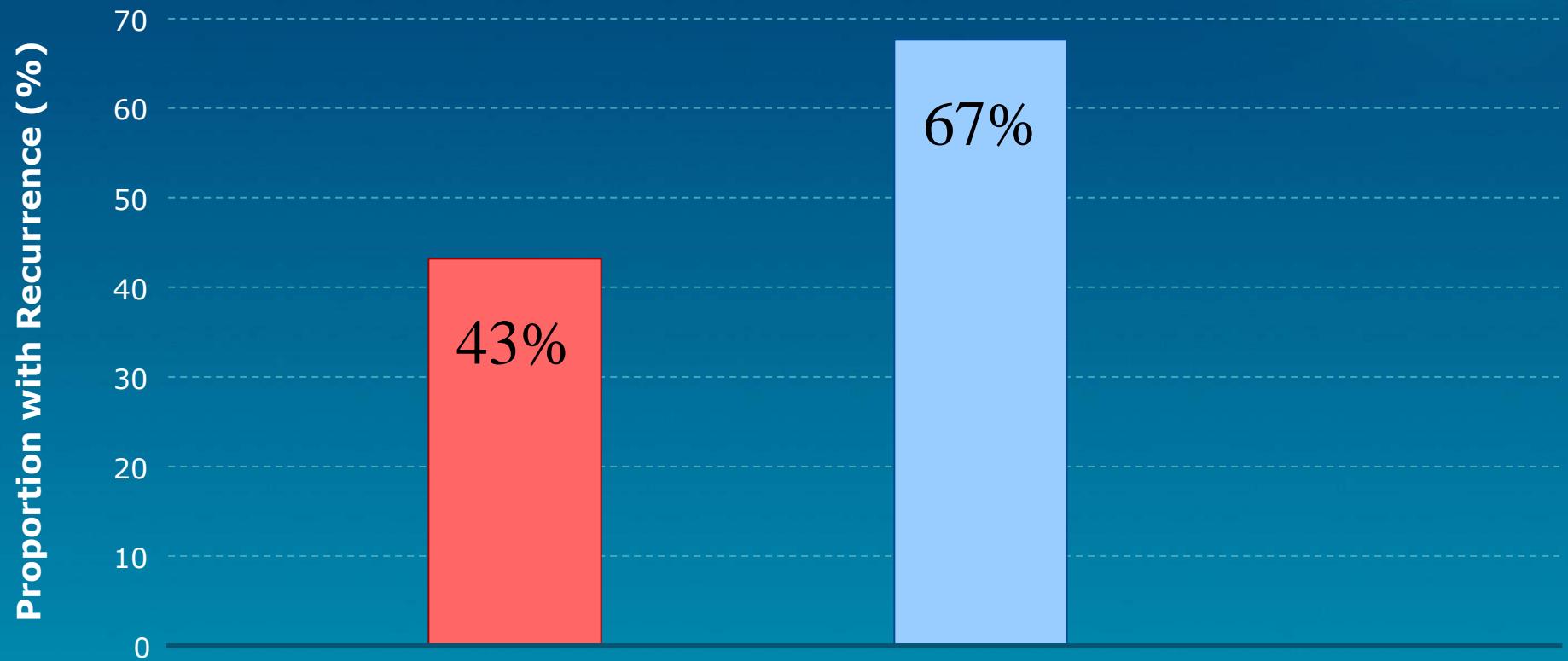


- ✓ In the future, it is to be hoped that newer generation novel AADs now on the horizon, such as multichannel blockers, atrial-specific agents, and gap junction modulators, will prove to be not only highly efficacious, but also better tolerated with no or minimal side effects, compared to currently available AADs, offering better pharmacotherapy of AF

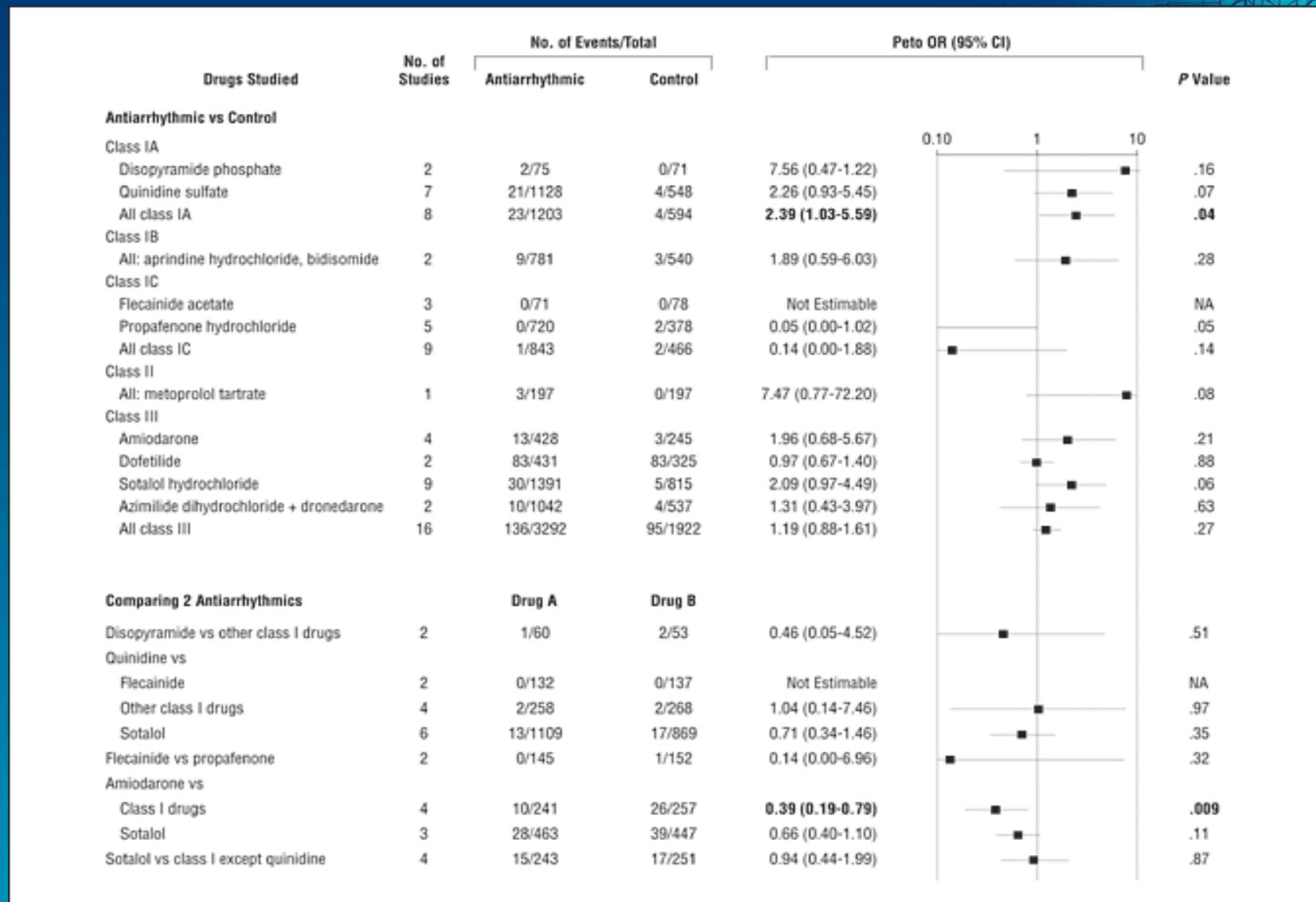
Prevention of recurrence in studies comparing AADs with placebo or no treatment

Drug/s studied	Studies (n)	Events No/Total		Peto Odds Ratio (95%CI)			P
		Anti-arrhythmic	Control	0.10	1	10	
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 Ic	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	363 / 431	0.30 (0.23 – 0.39)	-	<0.001
	Dronedarone	2	648 / 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 vs. Other Class I Drugs	2	26 / 60	27 / 53	0.76 (0.36 – 1.60)	-	ns	
Quinidine vs. Flecainide	2	103 / 132	99 / 137	1.38 (0.79 – 2.41)	-	ns	
Other Class I Drugs	4	176 / 258	168 / 268	1.30 (0.90 – 1.87)	-	ns	
Sotalol	6	715 / 1109	556 / 869	0.92 (0.76 – 1.11)	-	ns	
Flecainide vs. Propafenone	2	49 / 145	56 / 152	0.87 (0.54 – 1.40)	-	ns	
Amiodarone vs. Class I Drugs	5	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 vs. 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	

Pooled Recurrence Rates of AF at 1 year in patients treated with AADs



Overall Mortality associated with AADs



Implications



- ✓ The increased mortality of AADs due to their adverse effects probably nullifies the potential beneficial effects on survival of maintenance of sinus rhythm with these drugs.

Trial	Rate vs Rhythm Trials		n	Age, y	Mean Follow-up	Sinus rhythm (%)	Warfarin (%)	Thrombo-embolic complications %	Mortality %
PIAF									
Rate control	125	61			12m	10	100	NR	1.6
Rhythm control	127	60				56	100	NR	1.6
AFFIRM									
Rate control	2027	70			42m	35	85	6	21
Rhythm control	2033	70				63	70	7.5	24
RACE									
Rate control	256	68			27m	10	96-99	5.5	17
Rhythm control	266	68				39	86-99	7.9	13
STAF									
Rate control	100	65			22m	0	NR	0.6	5.0
Rhythm control	100	66				NR	NR	3.1	2.5
Hot Cafe									
Rate control	101	61			20m	NR	74	1	1.0
Rhythm control	104	60				63.5	NR	2.9	2.9
AF-CHF									
Rate control	694	67			37m	30-41	92	4	33
Rhythm control	682	66				73	88	3	32
J-RHYTHM									
Rate control	404	64.5			19m	44	59	2.9	0.7
Rhythm control	419	65				73	60	2.3	1.0

Modified from Falk, RH. *Circulation* (2005) 111: 3141