

En Que Pacientes Elijo Dronedarona?

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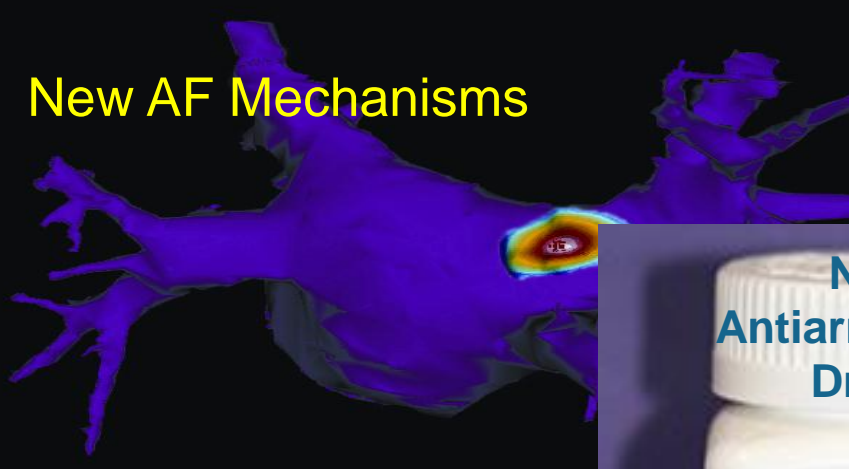


Conflicts of Interest

- ❖ Research Grants: Biosense Webster, Boston Scientific, Medtronic, St. Jude Medical, Transoma, Juan Valdez Café de Colombia, Other Undisclosed Colombian Pharmaceutical Companies!
- ❖ Honorarium: Biosense Webster, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Transoma, Astra Zeneca, Boeringher Ingelheim, Procaps, Sanofi-Aventis, Merck, Servier.
- ❖ Advisory Boards: Medtronic, Biosense Webster, Boston Scientific, Biotronik, Transoma, Schering Plough, Boeringher Ingelheim, Sanofi Aventis, Procaps, Biocaps, Servier
- ❖ I have no stock options under my name... all under Dr. Stuart Connolly's & Salim Yusuf's names! (AIG, Merryll Lynch)
- ❖ I have received Pens, Bags, Memory sticks, tickets to ball games, hockey games, soccer games, invitations for dinner, drinks and other undisclosed entertainment.
- ❖ Nonetheless... I do have my own unbiased opinions!

Recent Developments

New AF Mechanisms



New Oral Anticoagulants

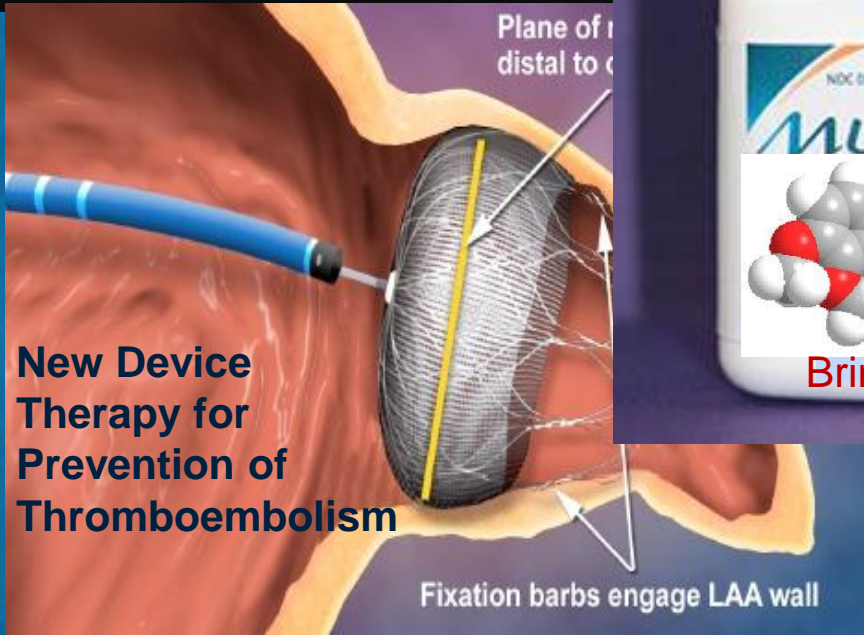


New Antiarrhythmic Drugs

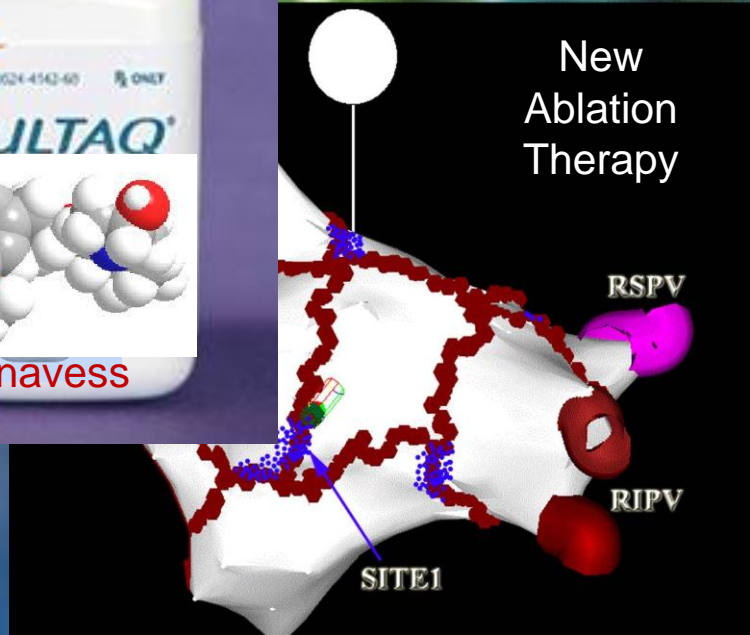


Brinavess

New Device Therapy for Prevention of Thromboembolism



New Ablation Therapy



Caso

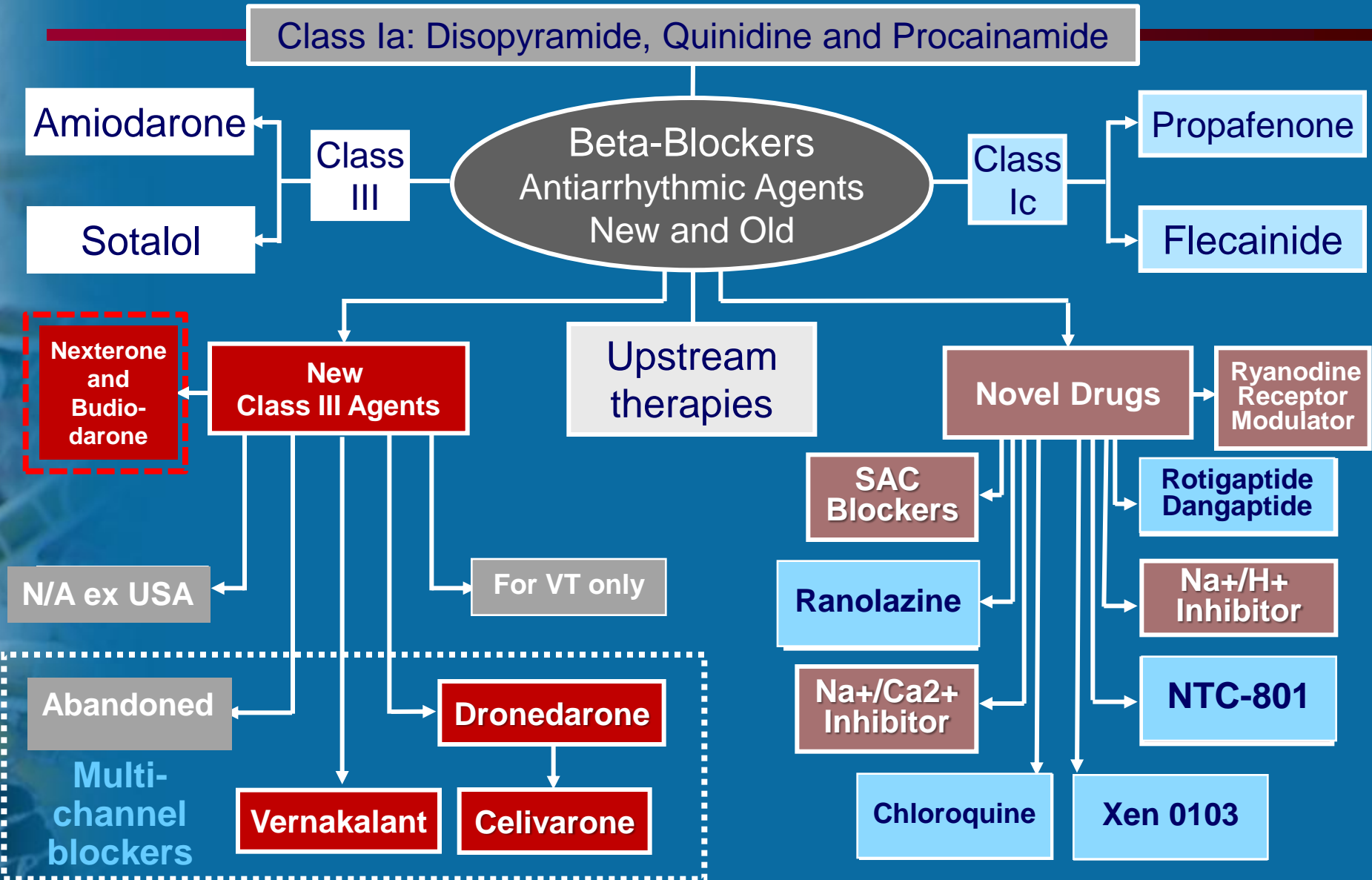
- ◆ Paciente con ECG precedidos por palpitaciones de 3 km de caminata rápida.

DOB:	26/02/1912(100)
Gender:	Female



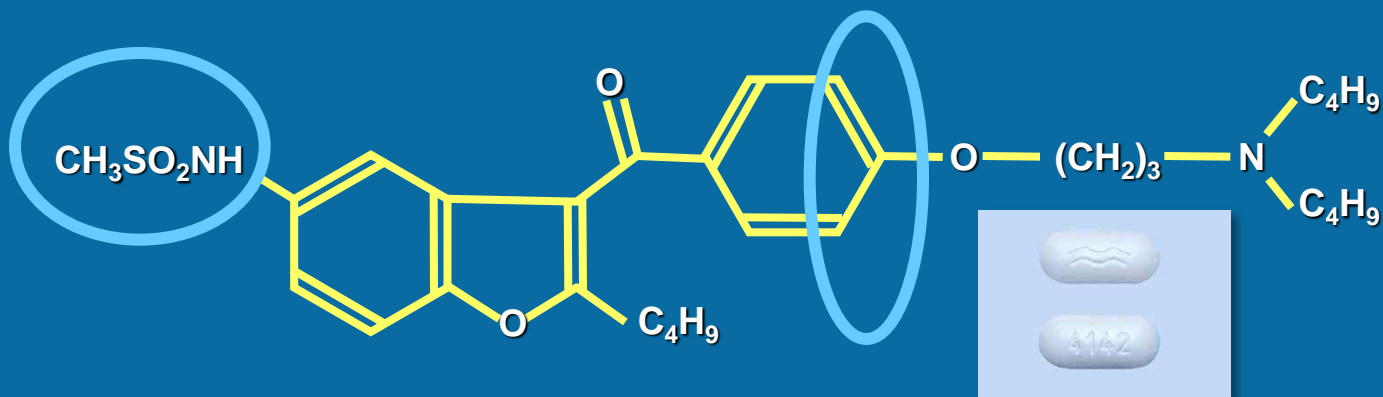
- ◆ No recibe medicaciones fuera de ASA.

Antiarrhythmic medical therapies



Adapted from Savelieva I, et al. *Europace*. 2008;10:647-65

Dronedarone

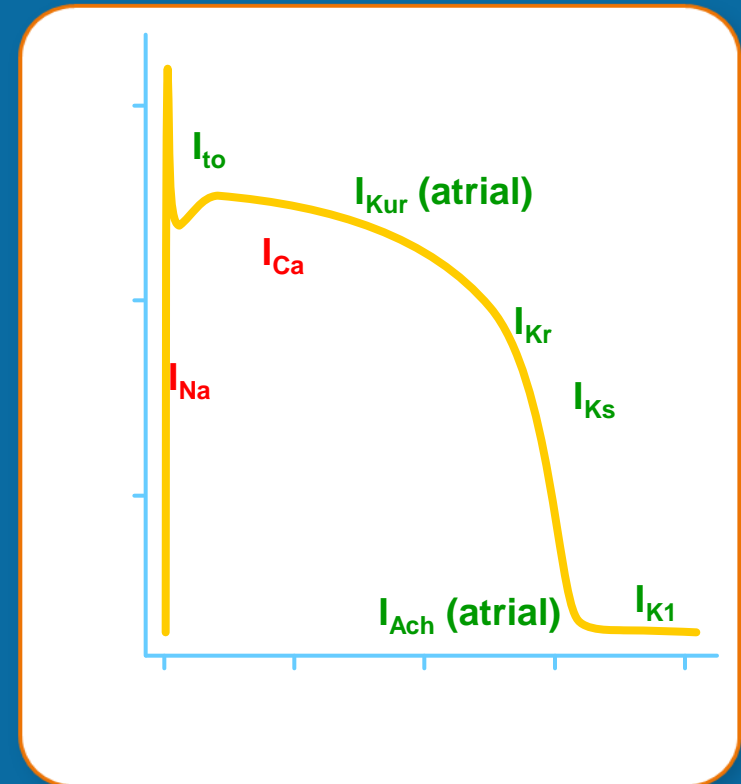


- Amiodarone-like compound lacking iodine
- Similar electrophysiological properties
- No evidence of thyroid or pulmonary toxicity
- 24-hour half-life
- Food effect (2–3 x increase in plasma levels)
- Extensive 1st pass metabolism (CYP450 3A4)
- 15% bioavailability

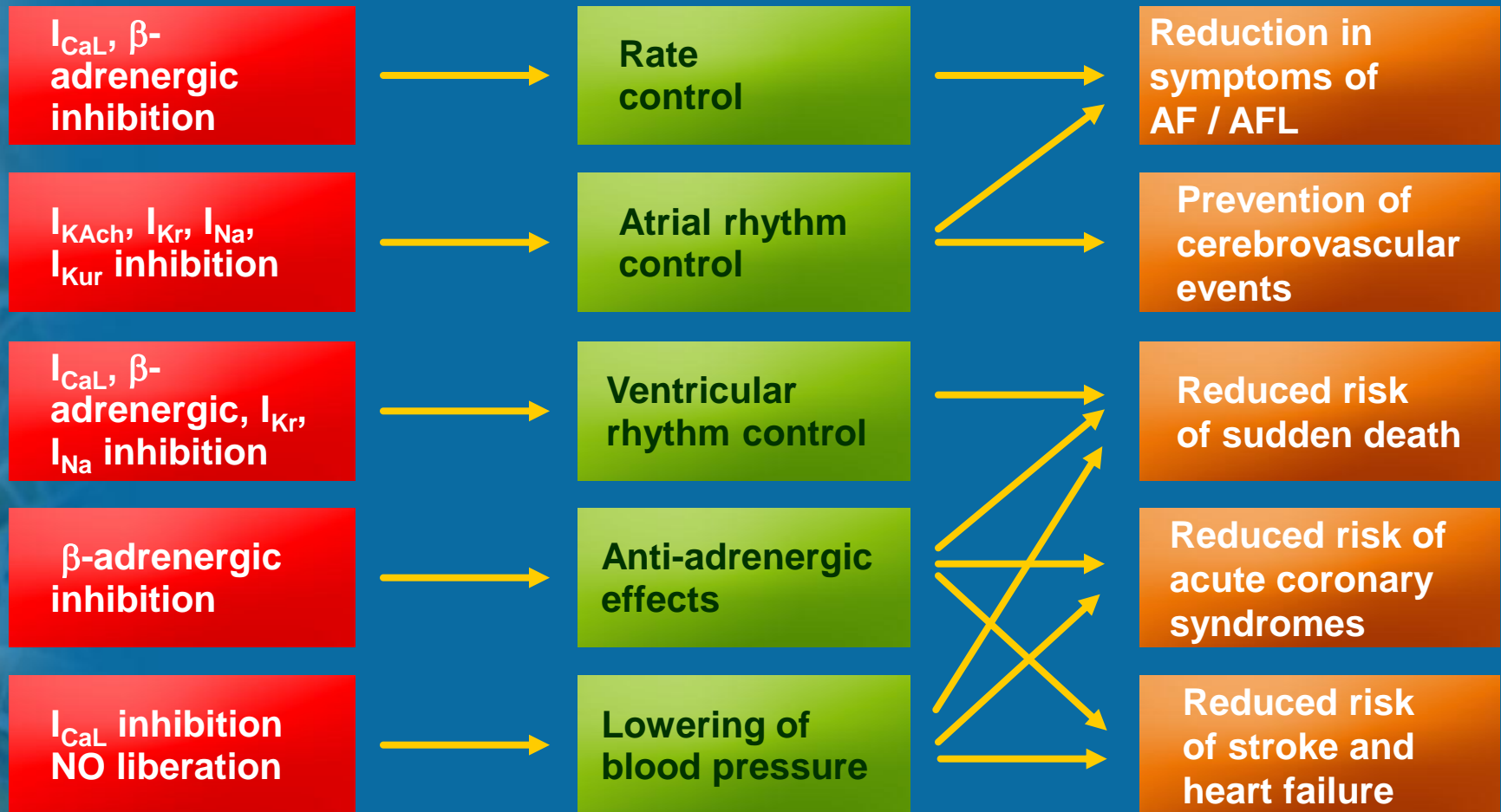


Dronedarone is a multichannel blocker

- Dronedarone Possesses Electrophysiologic Characteristics of all Four Vaughan Williams Classes¹
 - Outward currents
 - **I_{Kr}**: rapidly activating delayed rectifier potassium current
 - **I_{Ks}**: slowly activating delayed rectifier potassium current
 - **I_{K1}**: inward rectifier potassium current
 - **I_{to}**: transient outward current
 - **I_{K(Ach)}**: muscarinic receptor-operated K⁺ current (atria)
 - Inward currents
 - Fast sodium currents
 - Calcium channel antagonist
- Dronedarone has anti-fibrillatory effects in the ventricles and atria in animals²

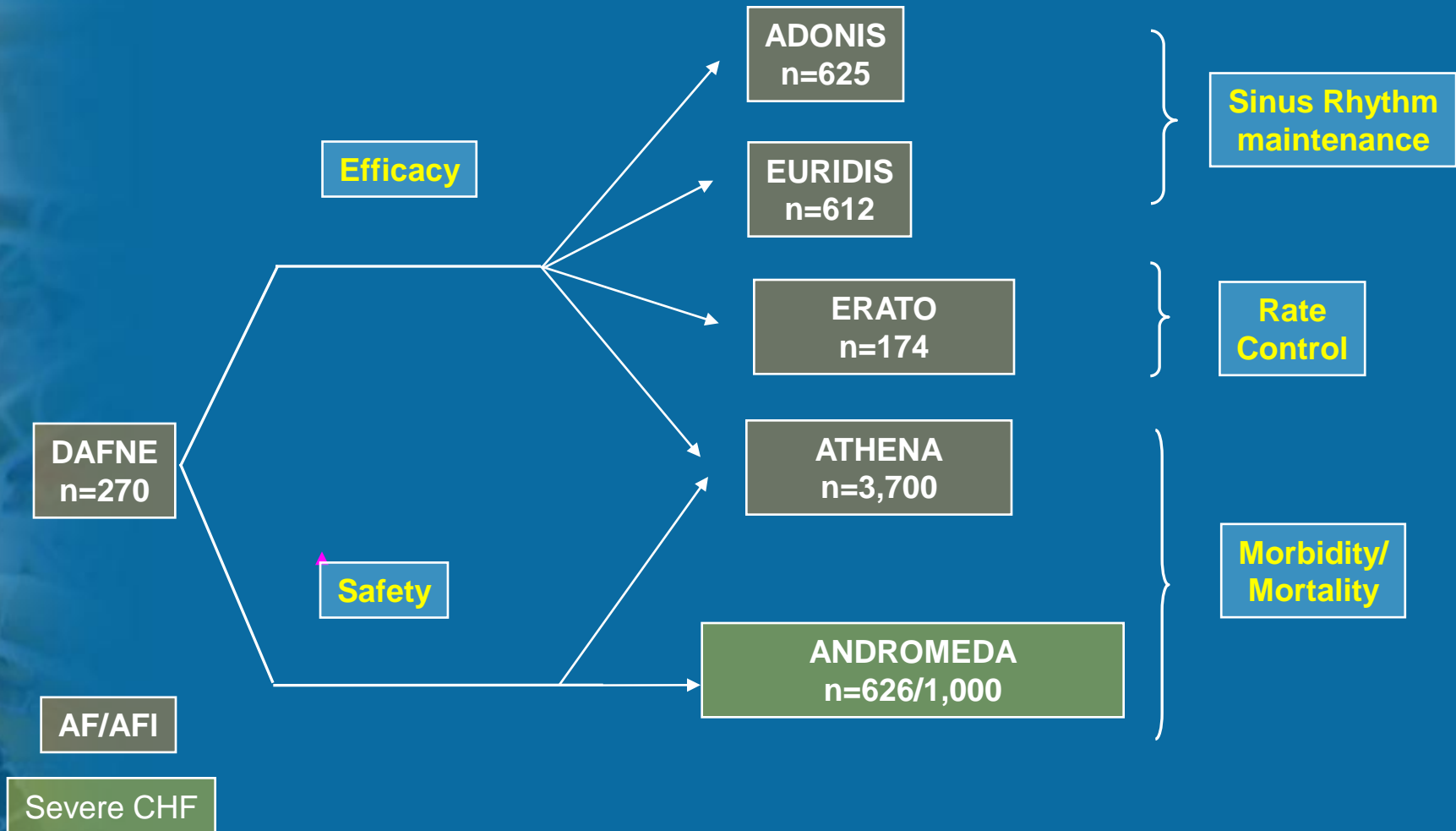


Dronedarone: Array of pharmacological effects and possible links with clinical benefits

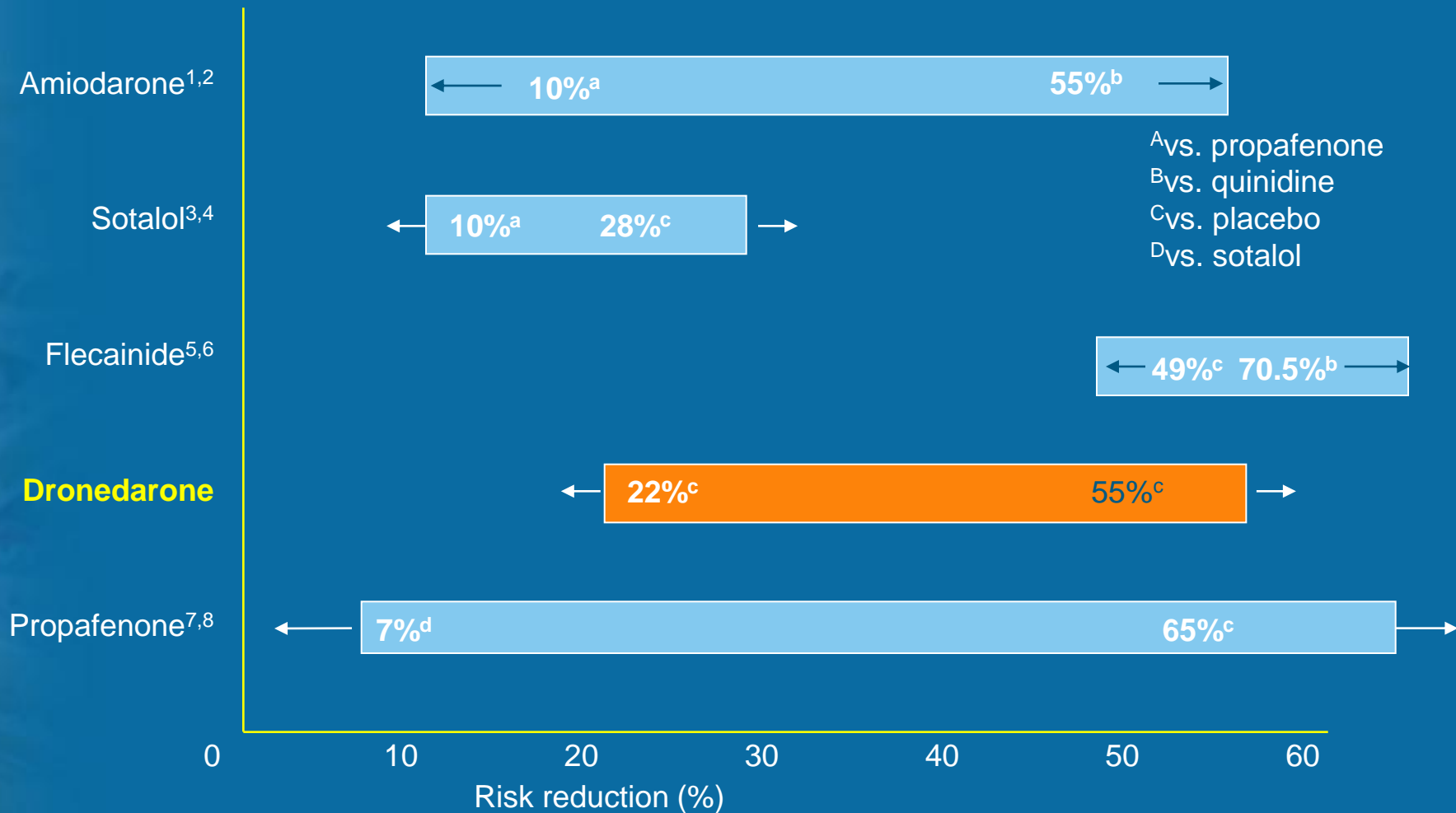


Dronedronone Clinical Overview

One of the Largest Clinical Trial Programs Ever Done in AF/AFL

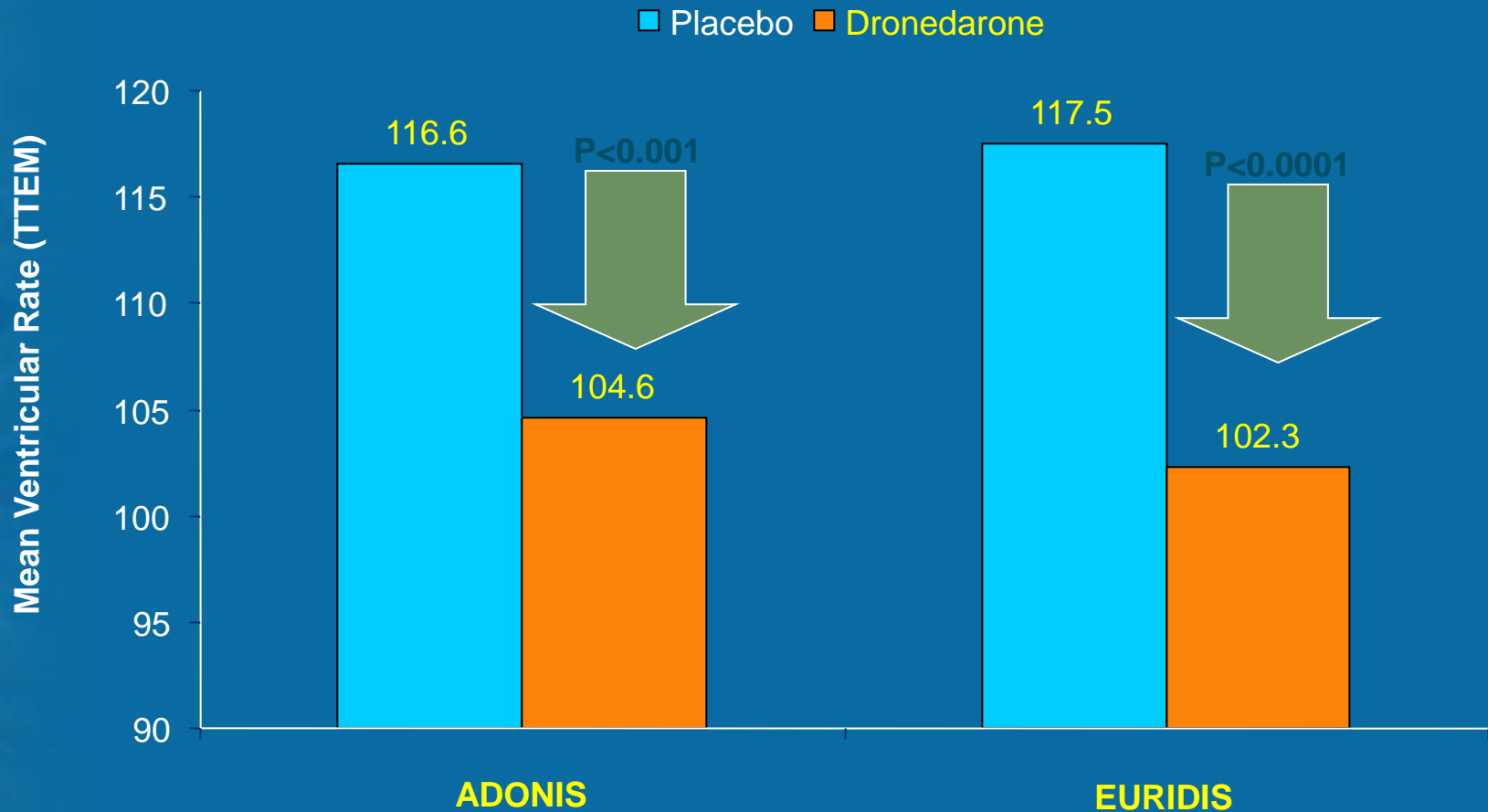


Range of Sinus Rhythm Maintenance Relative to Comparator Drugs

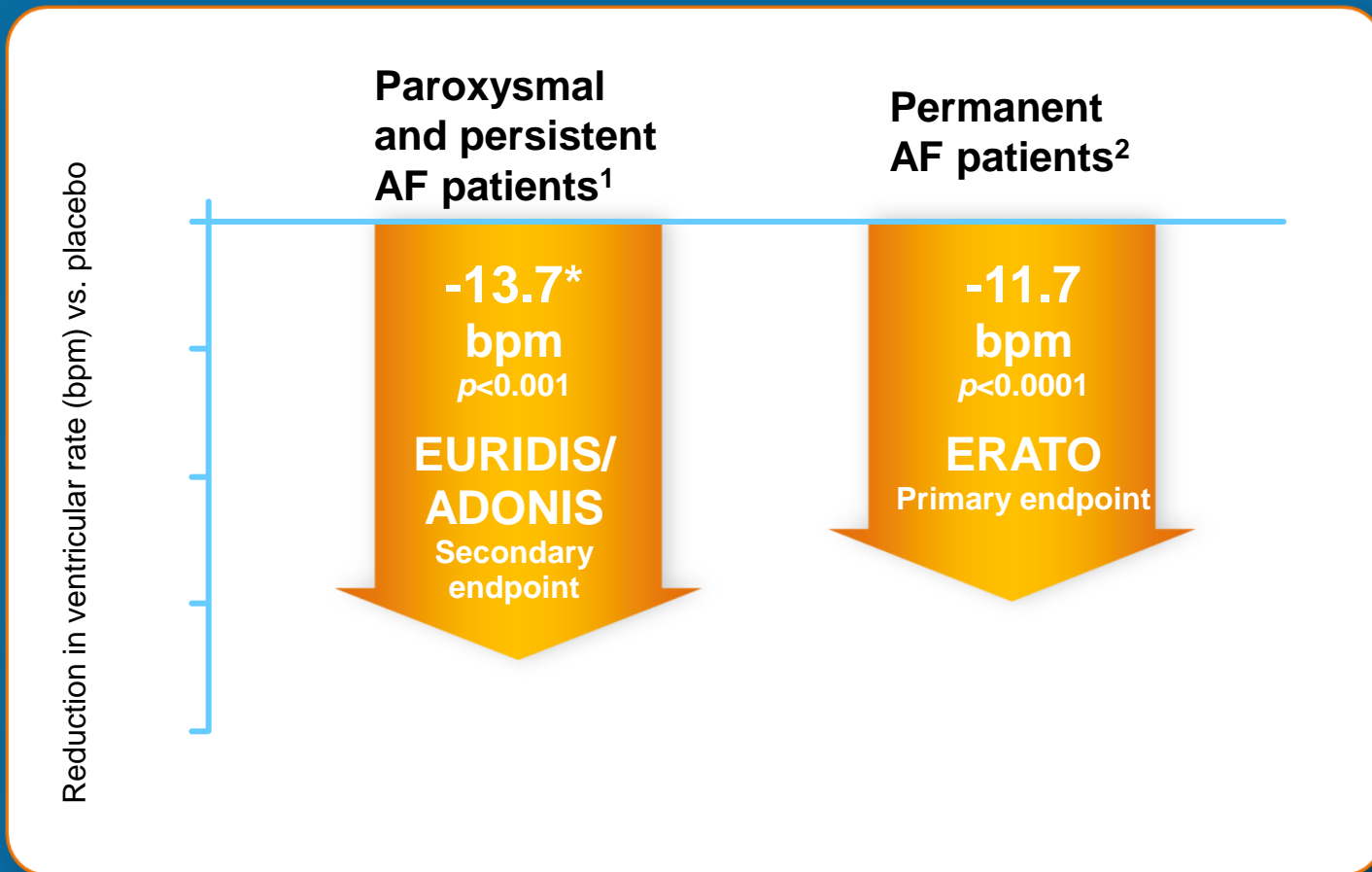


1. Kochiadakis GE, et al. *Chest* 2004;125:377–383. 2. Kerin NZ, et al. *Arch Intern Med* 1996;156:49–53. 3. *European Heart Journal* 2004;25:1385–1394. 4. Gosselink AT, et al. *JAMA* 1992;267:3289–3293. 5. Naccarelli GV, et al. *Am J Cardiol* 1996;77: 53A–9A. 6. Van Gelder IC, et al. *Am J Cardiol* 1989;64:1317–1321. 7. Reimold SC, et al. *Am J Cardiol* 1993;71:558–563. 8. Pritchett E, et al. *Am J Cardiol* 2003;92:94–946.

EURIDIS and ADONIS: Dronedarone Reduces Significantly and Consistently Ventricular Rate at First AF/AFL Recurrence



Dronedarone reduces ventricular rate across the spectrum of AF patients



Primary endpoint EURIDIS/ADONIS : time to first AF/AFL recurrence

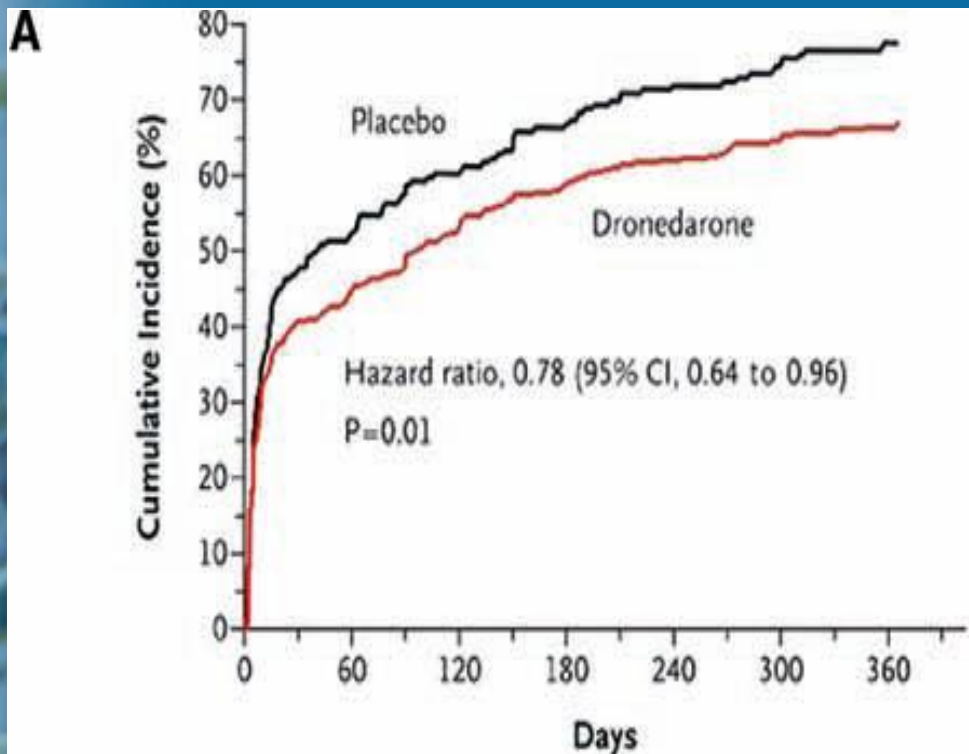
22%/27% reduction in relative risk ($p=0.01/p=0.002$)

* MULTAQ™ : 103.4 bpm vs. Placebo: 117.1 bpm

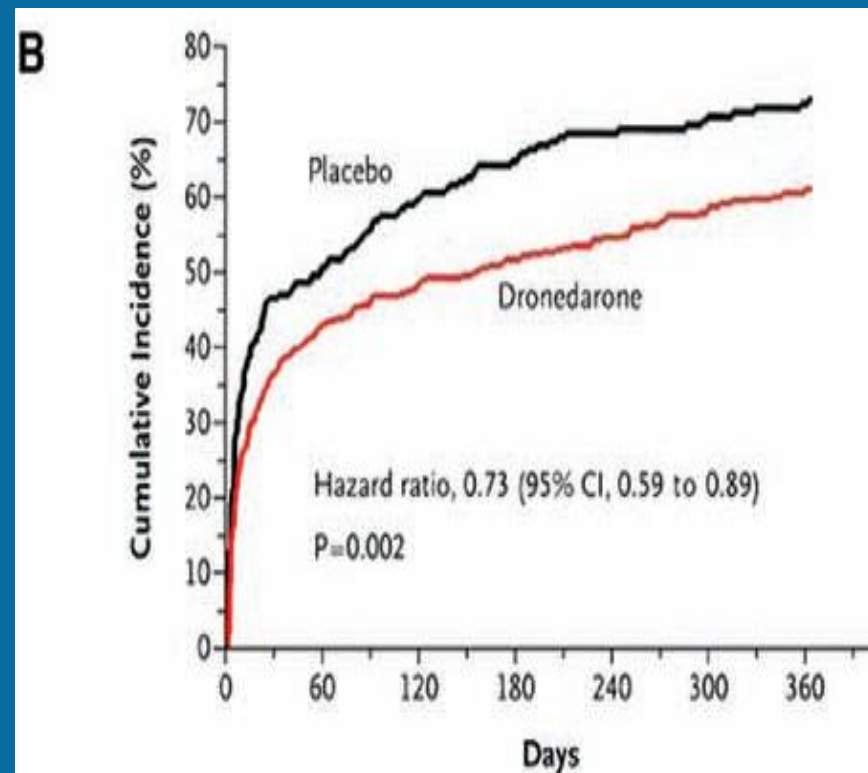
1. Singh BN et al. *N Engl J Med* 2007;357:987-99.

2. Davy et al. *Am Heart J* 2008;156:527.e1-527.e9.

Dronedarone EURIDIS & ADONIS

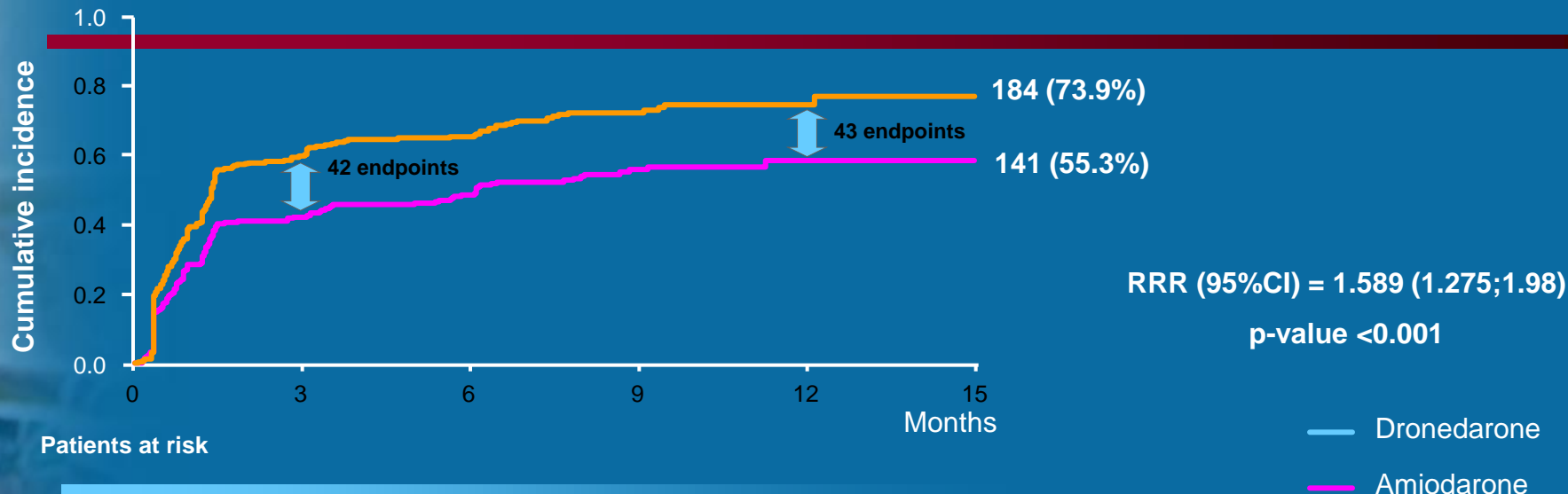


No. at Risk	0	60	120	180	240	300	360
Placebo	201	106	96	79	66	54	41
Dronedarone	411	239	222	189	164	145	125



No. at Risk	0	60	120	180	240	300	360
Placebo	208	105	96	77	67	58	49
Dronedarone	417	260	228	200	183	162	137

Dyonisios: Primary Endpoint: More AF Events But Less Early Discontinuation With Dronedarone



Patients at risk

Time (Months)	0	3	6	9	12	15
Dronedarone	249	99	84	40	12	0
Amiodarone	255	146	126	61	13	0

	Dronedarone (n=249)	Amiodarone (n=255)
Number of patients with endpoint	184 (73.9%)	141 (55.3%)
ECG documented AF endpoint	158 (63.5%)	107 (42.0%)
Documented AF after conversion	91 (36.5%)	62 (24.3%)
Unsuccessful electrical cardioversion	29 (11.6%)	16 (6.3%)
No spontaneous conversion and no electrical cardioversion on day 10 to day 28	38 (15.3%)	29 (11.4%)
Premature study drug discontinuation	26 (10.4%)	34 (13.3%)
Lack of efficacy	1 (0.4%)	0
Intolerance	25 (10.0%)	34 (13.3%)

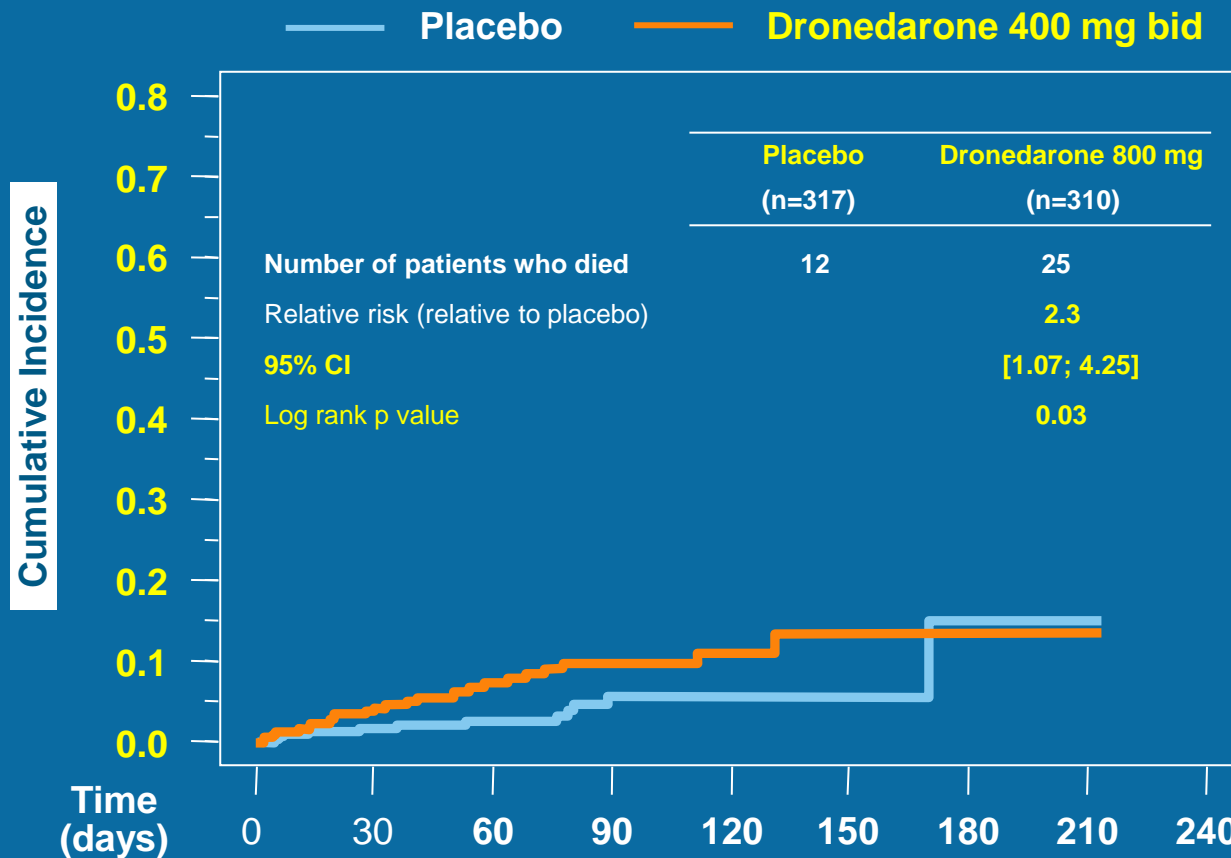
ANDROMEDA – inclusion criteria

- Consecutive hospitalized patients ≥ 18 years
- New/worsening HF with at least another episode of decompensation corresponding to NYHA class III–IV within the last month, and treated with a diuretic
- WMI < 1.2 ~ LVEF < 0.35



Randomized < 7 days after hospital admission

ANDROMEDA: all-cause mortality



ANDROMEDA study.
NEJM 2008.

ANDROMEDA: cause of death

Table 2. Cause of Death.

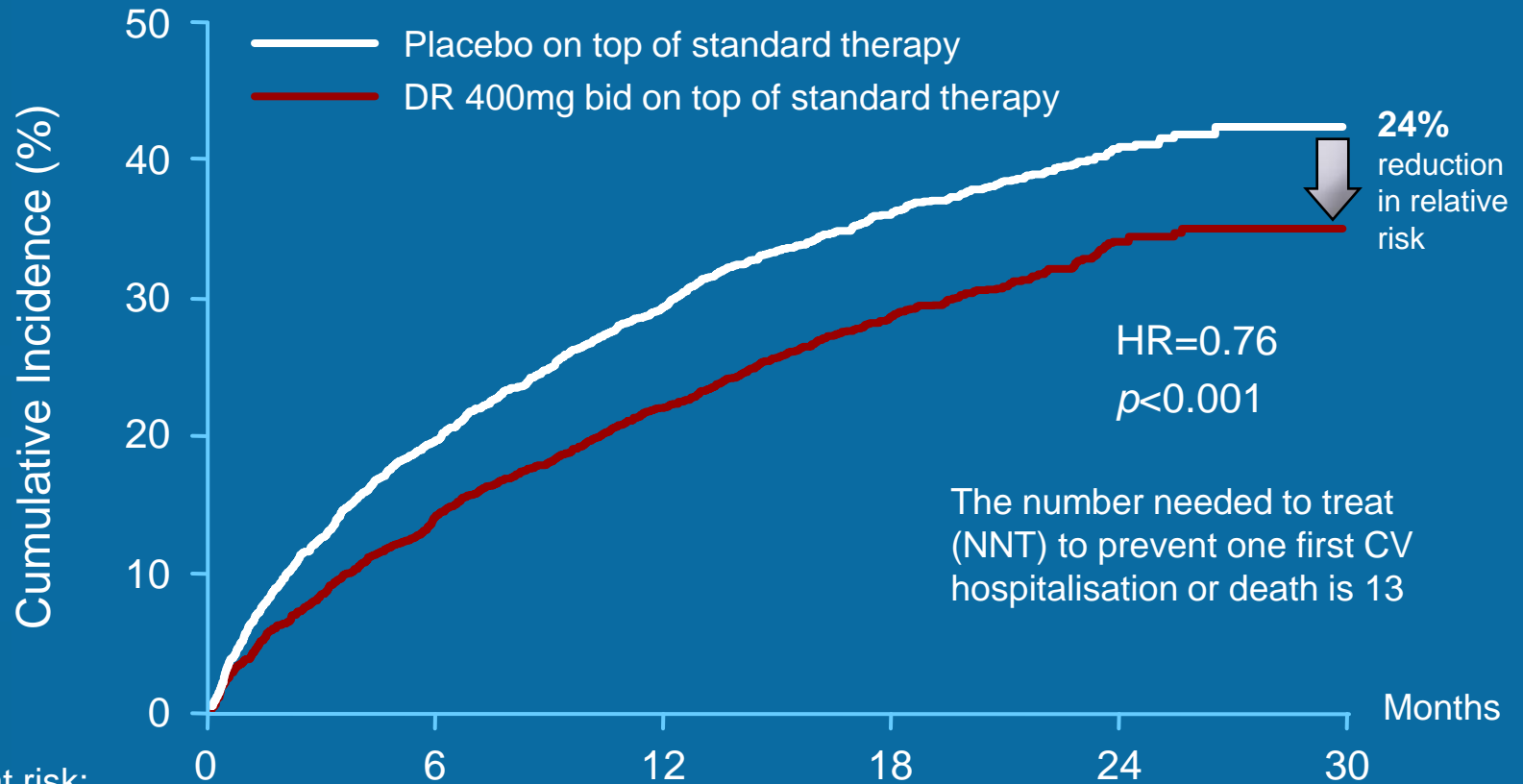
Cause	Dronedarone Group (N=310)	Placebo Group (N=317)
	<i>no. (%)</i>	
Cardiovascular	24 (7.7)	9 (2.8)
Myocardial infarction	0	2 (0.6)
Progressive heart failure	10 (3.2)	2 (0.6)
Documented arrhythmia	6 (1.9)	2 (0.6)
Other cardiovascular cause	3 (1.0)	0
Presumed cardiovascular cause	5 (1.6)	3 (0.9)
Arrhythmia or sudden death*	10 (3.2)	6 (1.9)
Noncardiovascular	1 (0.3)	3 (0.9)
Total	25 (8.1)	12 (3.8)

Increased in patients with very low EF (WMI < 1)

ATHENA: Patient Characteristics

	Placebo (N=2327)	Dronedaronone (N=2301)	All patients (N=4628)
Age (mean; SD, years)	72 ± 9.0	72 ± 8.9	72 ± 9.0
Female gender	1038 (45%)	1131 (49%)	2169 (47%)
AF/AFI at baseline	586 (25%)	569 (25%)	1155 (25%)
Structural heart disease	1402 (61%)	1330 (58%)	2732 (60%)
Hypertension	1996 (86%)	1999 (87%)	3995 (86%)
Coronary heart disease	737 (32%)	668 (29%)	1405 (30%)
Valvular heart disease	380 (16%)	379 (17%)	759 (16%)
Non-ischemic cardiomyopathy	131 (6%)	123 (5%)	254 (6%)
History of CHF NYHA II/III	515 (22%)	464 (20%)	979 (21%)
LVEF < 0.45	285/2281 (13%)	255/2263 (11%)	540/4544 (12%)
LVEF < 0.35	87/2281 (4%)	92/2263 (4%)	179/4544 (4%)
Lone atrial fibrillation	139 (6%)	140 (6%)	279 (6%)
Pacemaker	243 (10%)	214 (9%)	457 (10%)

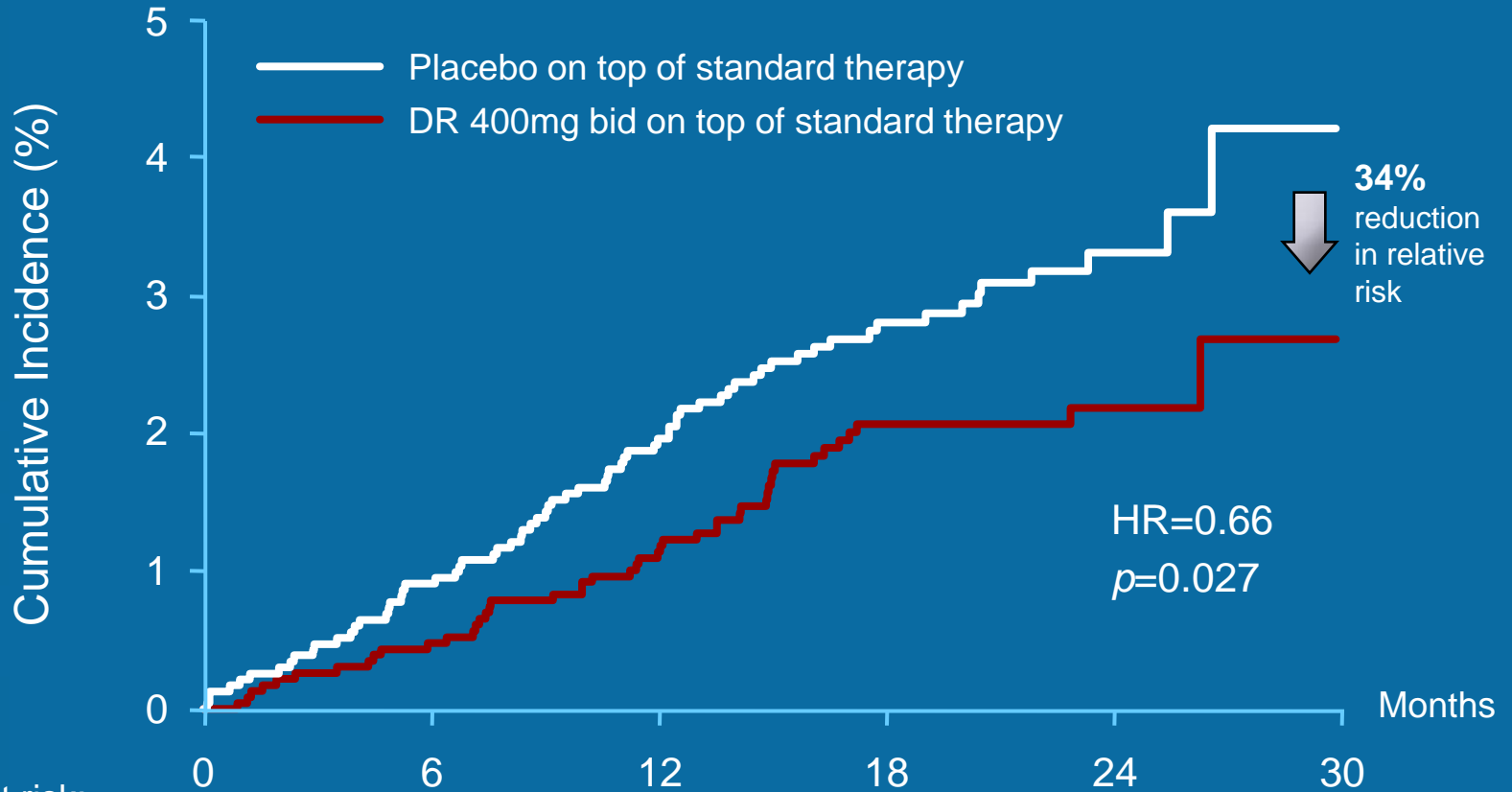
ATHENA: Primary Outcome: Risk of unplanned CV hospitalisation or death from any cause



Patients at risk:

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

Dronedarone significantly reduced the relative risk of stroke by 34%



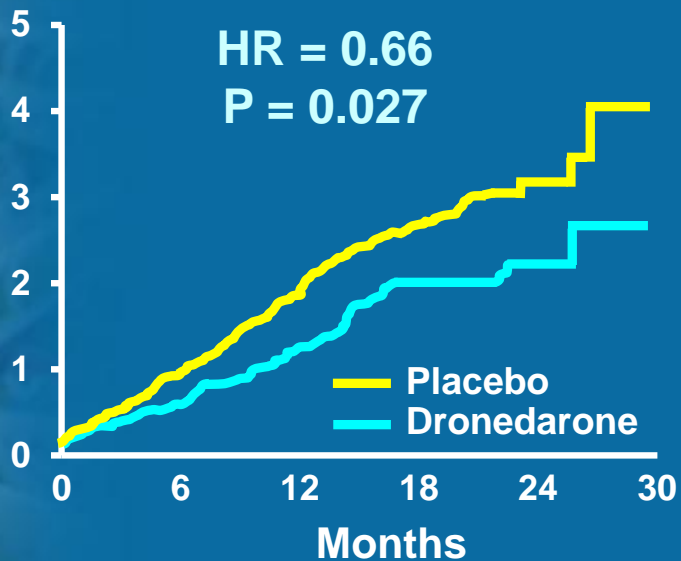
Patients at risk:

Placebo	2327	2275	2220	1598	618	6
DR 400mg bid	2301	2266	2223	1572	608	4

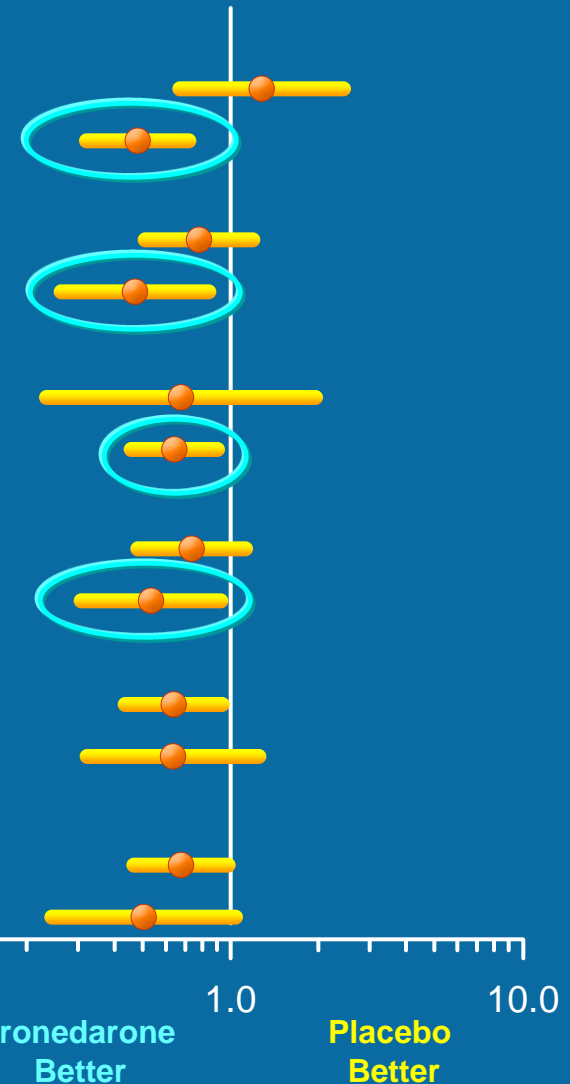
ATHENA: Incidence of Stroke

Post Hoc Analysis

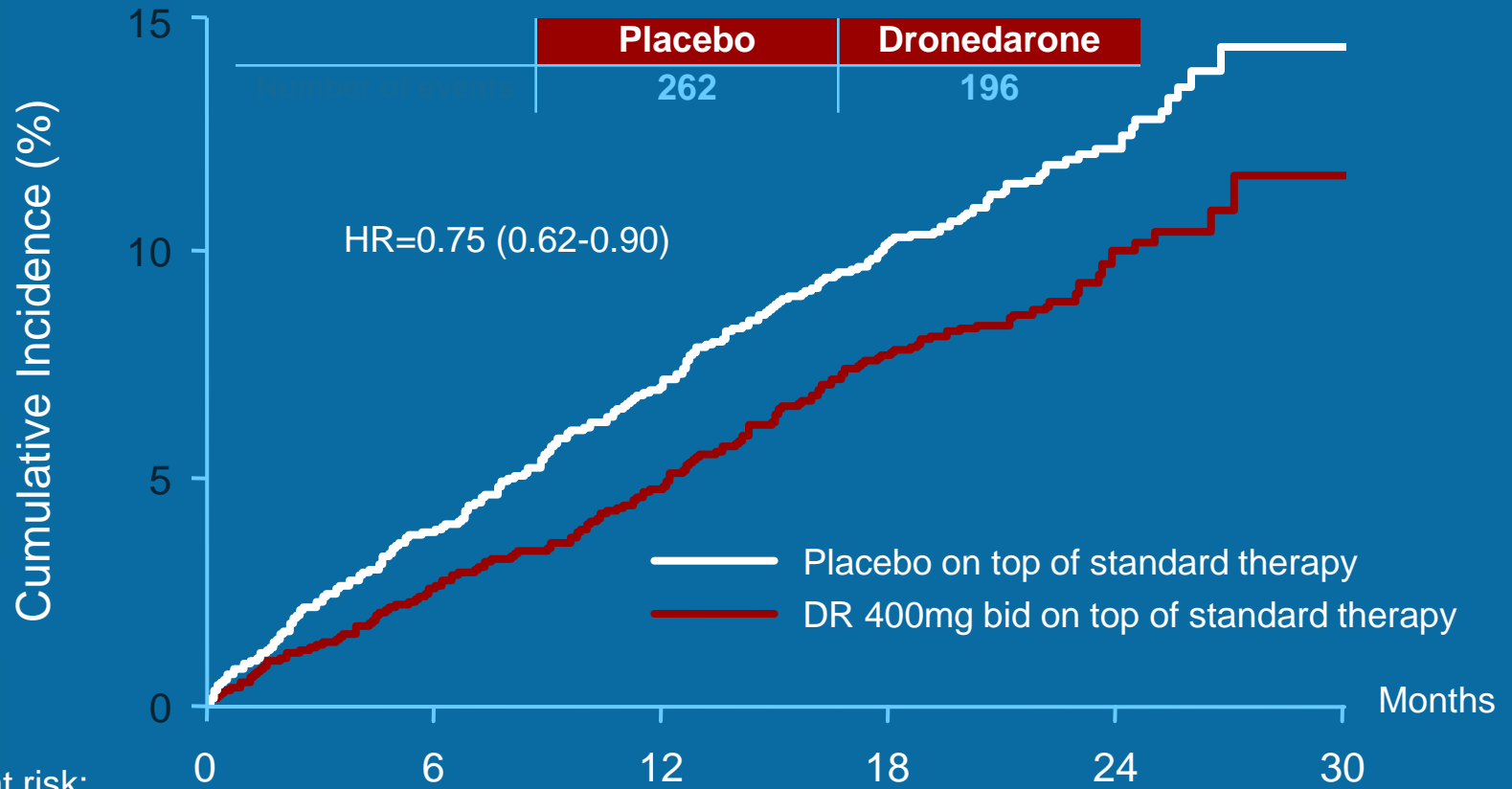
Cumulative incidence of stroke, %



CHADS₂ score
≤1
≥2
CHF
No
Yes
Hypertension
No
Yes
Age in years
<75
≥75
Diabetes mellitus
No
Yes
Stroke/TIA
No
Yes



Dronedarone significantly decreased risk of all-cause mortality, stroke and ACS by 25%



Patients at risk:

Placebo	2327	2240	2166	1547	599	6
DR 400mg bid	2301	2243	2193	1541	586	4

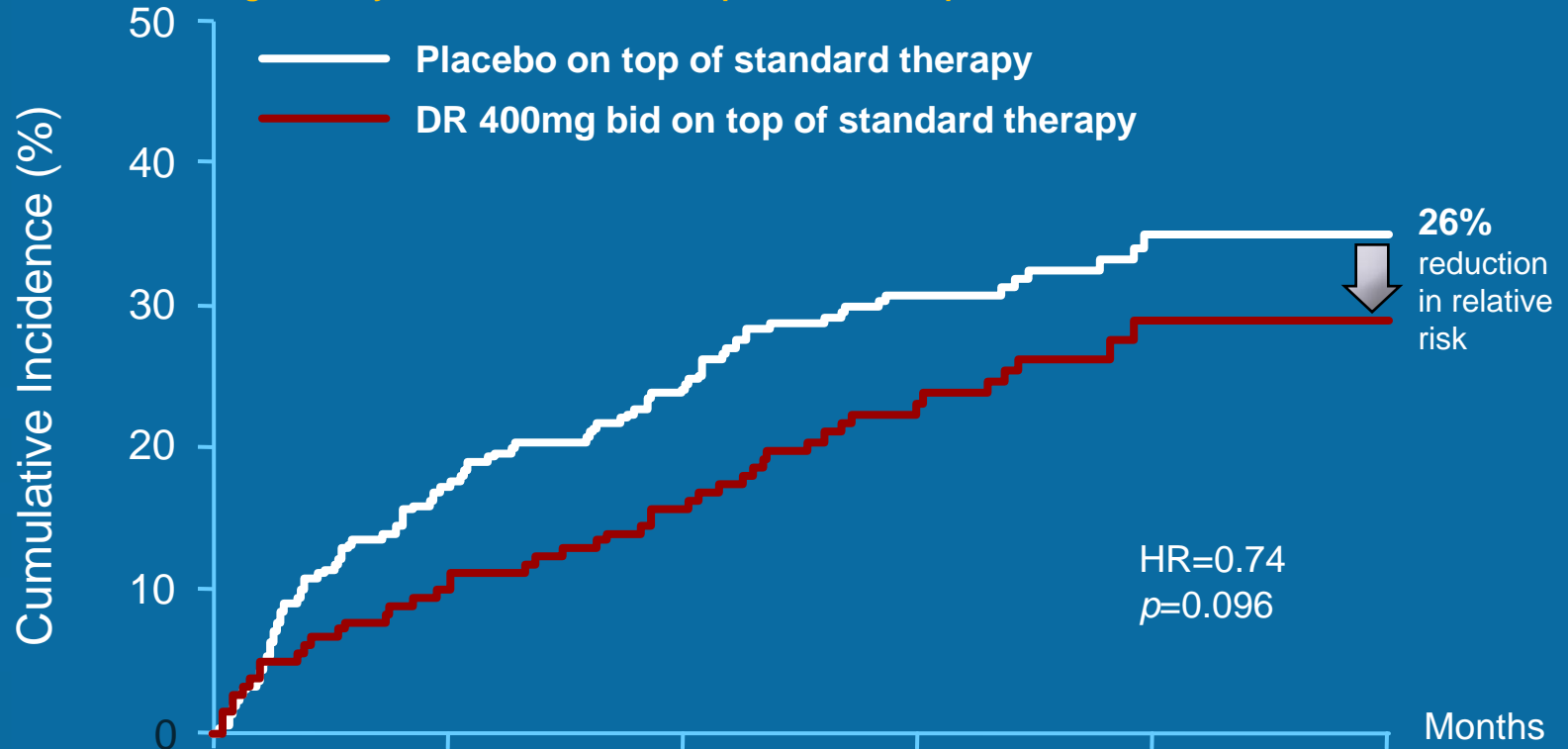
ATHENA:

Dronedarone significantly decreased risk of arrhythmic death by 45% and CV death by 29%

	Placebo n=2327	Dronedarone n=2301	HR	95% CI	<i>p</i> value
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

Benefits of dronedarone in 'permanent'* patients consistent with overall population

- Dronedarone Non-significantly Reduced the Risk of Unplanned CV Hospitalisation or Death in "Permanent" AF Patients



Patients at risk:

	0	6	12	18	24	30
Placebo	295	244	224	151	60	0
DR 400mg bid	178	160	150	110	47	1

Mean follow-up 21 ±5 months.
 Page R, et al. *AHA Scientific Sessions* 2008.
 Page R, et al. *Circulation*. 2008;118:S_827.

Benefits of dronedarone consistent in patients with heart failure and reduced LVEF versus overall population

Unplanned CV hospitalization or all-cause death

Patient Group	Placebo (n)	Dronedarone (n)	Hazard ratio	95% confidence interval	p value for interaction
Patients without CHF	1634	1629	0.76	0.68 - 0.86	0.22
Patients with CHF NYHA I/II	584	581	0.80	0.67 - 0.96	
Patients with CHF NYHA III	109	91	0.56	0.38 - 0.82	
Patients with LVEF ≤0.40	184	154	0.72	0.51 - 1.00	0.67
Patients with LVEF >0.40	2097	2109	0.77	0.69 - 0.85	

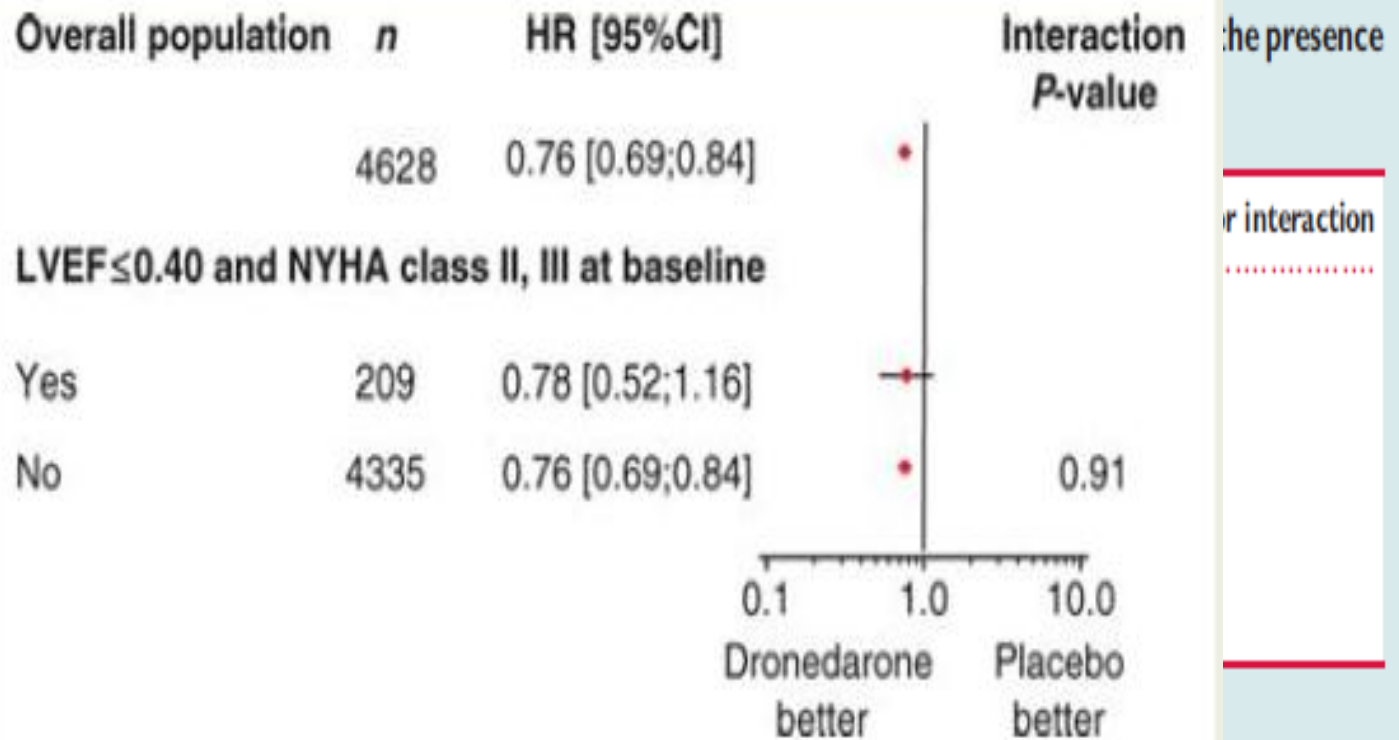
ATHENA exclusion criterion: recently decompensated CHF and CHF NYHA class IV

Dronedarone in patients with congestive heart failure: insights from ATHENA

Table 1 Ha
or absence of

Patient group
.....
Patients without
Patients with C
Patients with C
Patients with L
Patients with L

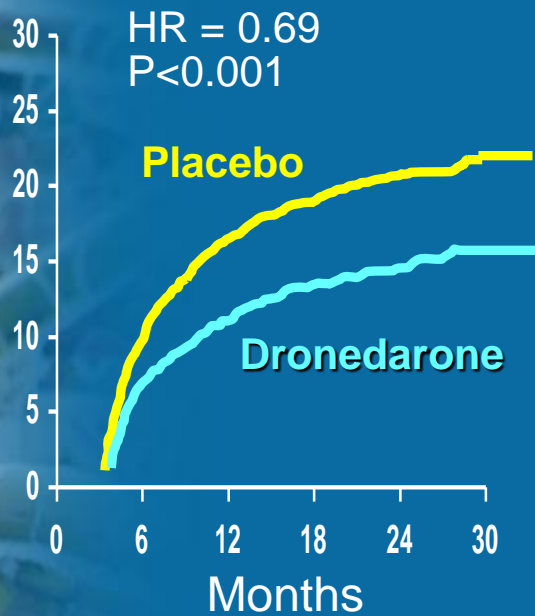
P, placebo; D, dro



ATHENA: ? an Antiarrhythmic Effect

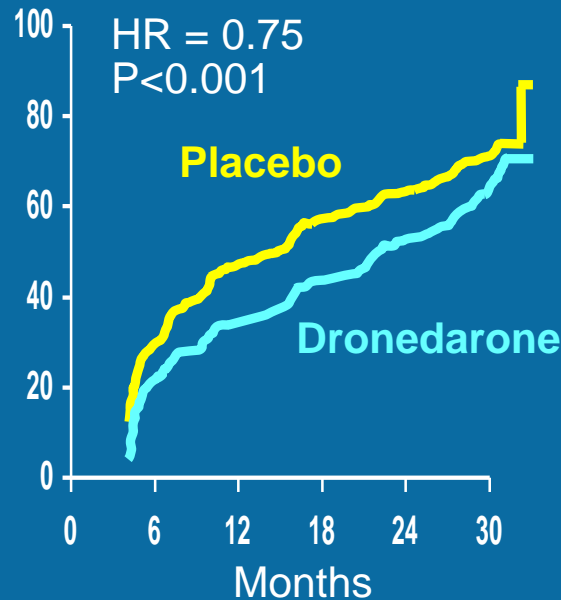
Time to 1st DCV

Cumulative incidence, %



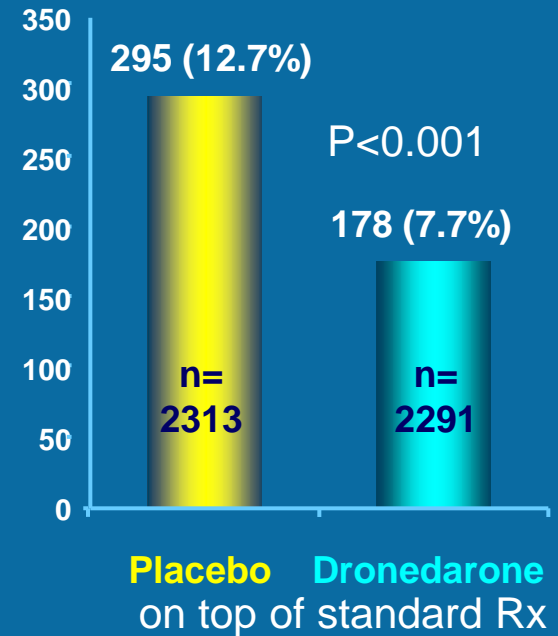
Time to 1st AF/AFL

Cumulative incidence of AF/AFL, %



No. in Permanent AF

Number of Patients



Dronedarone Efficacy Summary

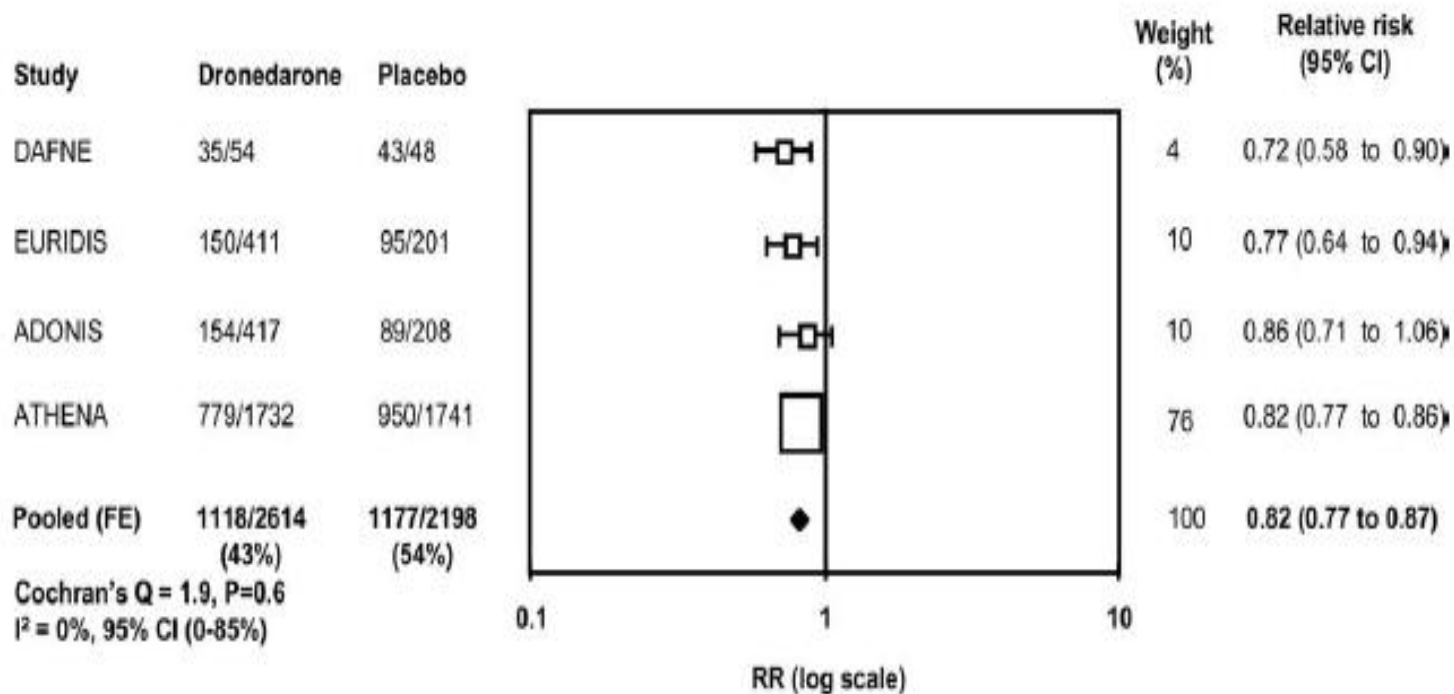
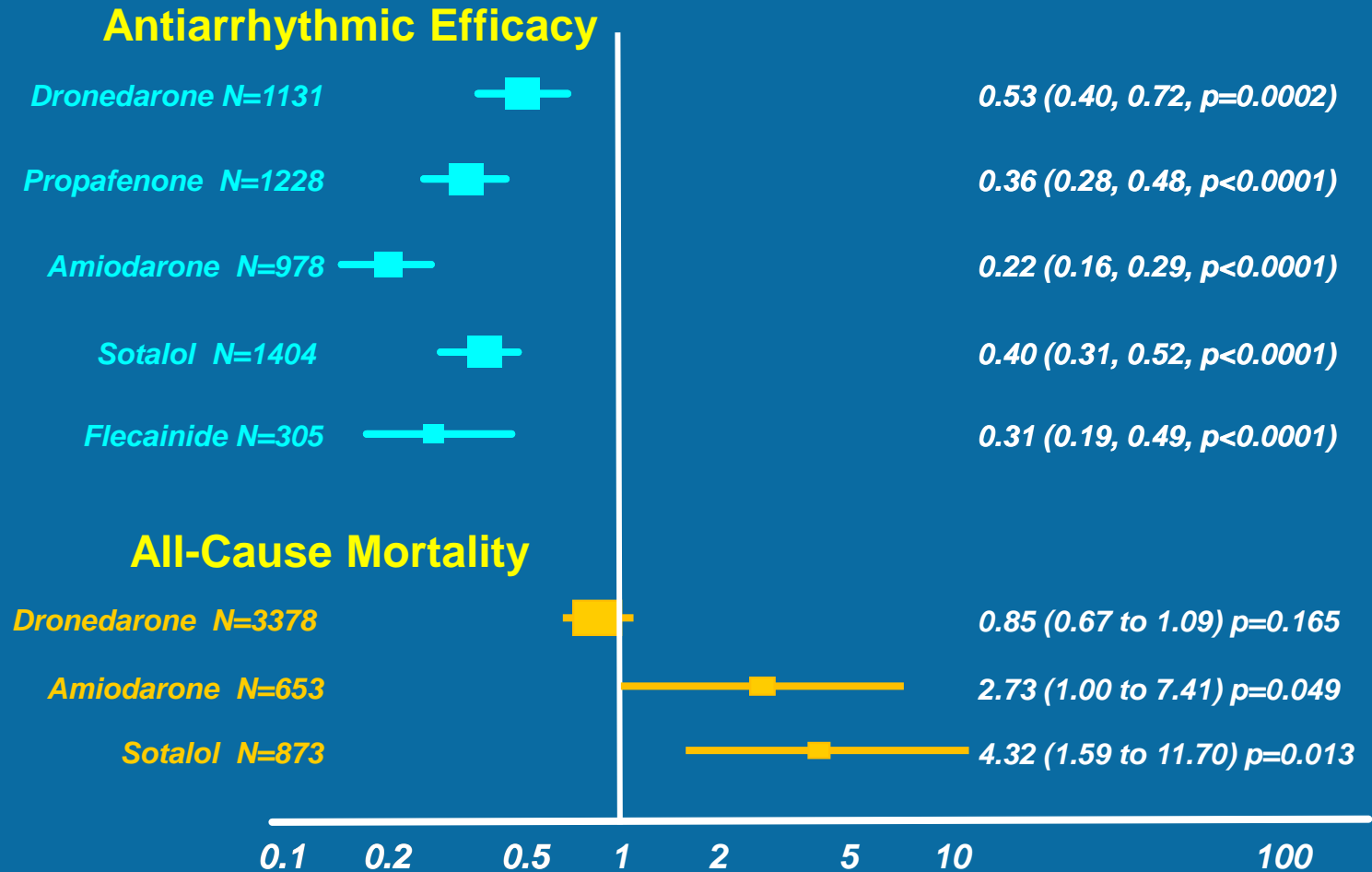


Figure 1 RR of AF Recurrence With Dronedarone Versus Placebo

AF Recurrence and All-Cause Mortality

Odds Ratios compared with Placebo



Permanent AF is associated with increased CV risk

- Permanent AF can develop over time among patients initially diagnosed with paroxysmal or persistent forms of the disease¹.
- Approximately 50 percent of patients with AF have permanent AF^{2, 3} which is associated with an increased rate of major adverse cardiovascular events⁴.

1. Kato T, Yamashita T, Sagara K, Linuma H, Fu L. Progressive Nature of Paroxysmal Atrial Fibrillation; Observations From a 14-Year Follow-up Study. *Circulation* 2004; 68:568-572
2. Levy, S Maarek M, Coumel P, et al., Characterisation of different subsets of atrial fibrillation in general practice in France: the ALFA study, *Circulation*, 1999;99:3028-35.
3. EU Intention to Rx study (Dec.08); US ATU Tracking (June 09)
4. Lloyd-Jones et al. Lifetime Risk for Development of Atrial Fibrillation: The Framingham Heart Study *Circulation*. 2004; 110:1042-1046.

Permanent AF is associated with a high risk of events

- Findings from Euro Heart survey*

Major adverse events during 1 year	First Detected (n=708) [n, proportion]	Paroxysmal (n=1170) [n, proportion]	Persistent (n=886) [n, proportion]		p-value
All cause death	43 (5.7)	43 (3.5)	27 (3.0)	100 (8.2)	<0.001
CV death	14 (1.9)	15 (1.3)	19 (2.1)	43 (3.6)	0.001
Ischemic stroke	9 (1.3)	22 (1.9)	11 (1.2)	19 (1.6)	0.582
TIA	5 (0.7)	9 (0.8)	12 (1.4)	30 (2.5)	0.001
Coronary artery disease	46 (6.6)	63 (5.6)	38 (4.3)	71 (6.1)	0.005
Heart failure	66 (9.5)	109 (9.6)	75 (8.5)	195 (16.6)	<0.001



Hoga

PALLAS: Objectives

- Primary

- To demonstrate the efficacy of dronedarone in patients with permanent atrial fibrillation and additional risk factors in preventing:

- Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death)
- First unplanned cardiovascular hospitalization or death from any cause

- Secondary

- To demonstrate the efficacy of dronedarone in preventing cardiovascular death
- To assess that dronedarone is well tolerated in this population

PALLAS: Sample Size Calculation on MACE Endpoints

1. Construction of a prognostic index to split the placebo ATHENA population in risk groups for the composite endpoint of stroke, ACS or CV death

	Low	Medium	High
Risk Factors	0 to 2	2 or 3	≥ 3

- Medium considered as the minimal population at risk in PALLAS

Treatment effect for CV death or ACS or stroke according level of risk

	Low risk (N= 681)	Medium risk (N= 810)	High risk (N= 836)
Number of events, n	28	59	130
Patient years at risk	1185	1382	1344
Cumulative incidence of events at 1 year [95% CI]	0.026(0.014-0.039)	0.045(0.030-0.059)	0.103(0.083-0.124)

- Placebo group event rate expected at one year = 4.5

Dronedarone in High-Risk Permanent Atrial Fibrillation

10.1056/NEJM081109867 NEJM.ORG

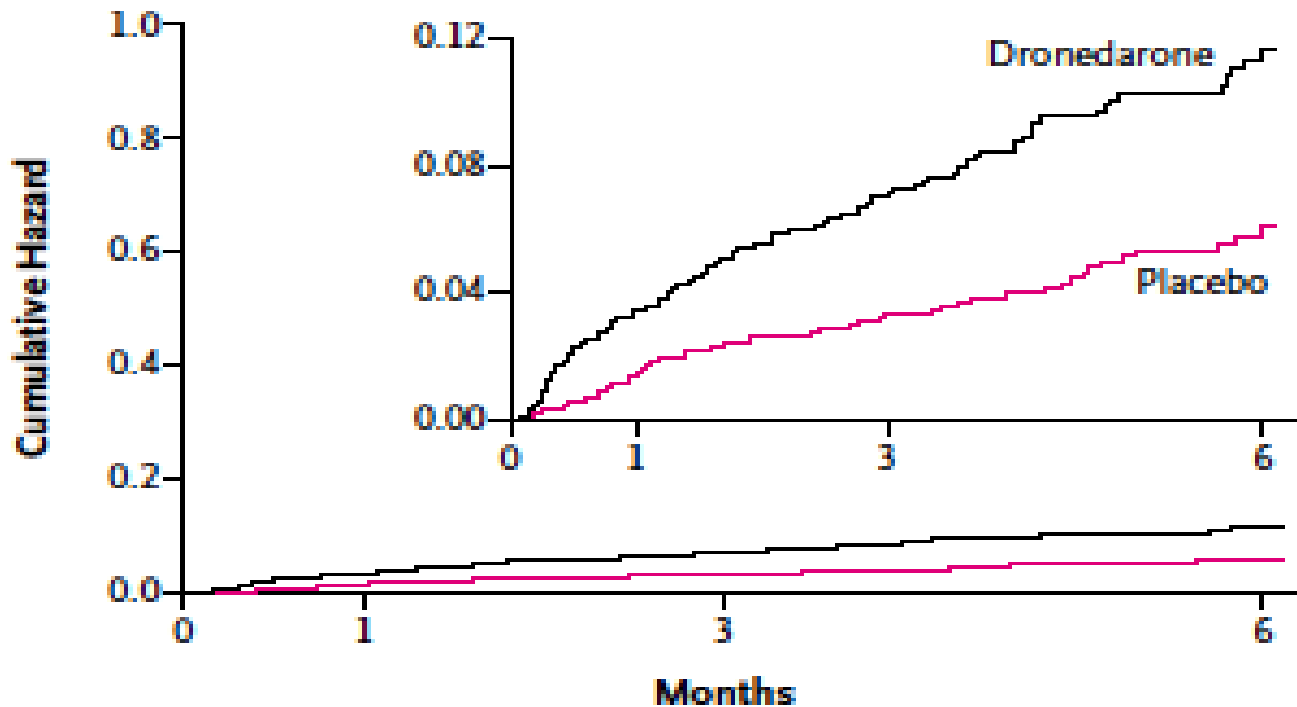
Table 1 Characteristics of the Patients at Baseline *

Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI) [†]	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any [‡]	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization [§]	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001
Duration of permanent atrial fibrillation >2 yr — no. (%)	115 (69.1)		114 (69.3)			

Dronedarone in High-Risk Permanent Atrial Fibrillation

10.1056/NEJM081109867 NEJM.ORG

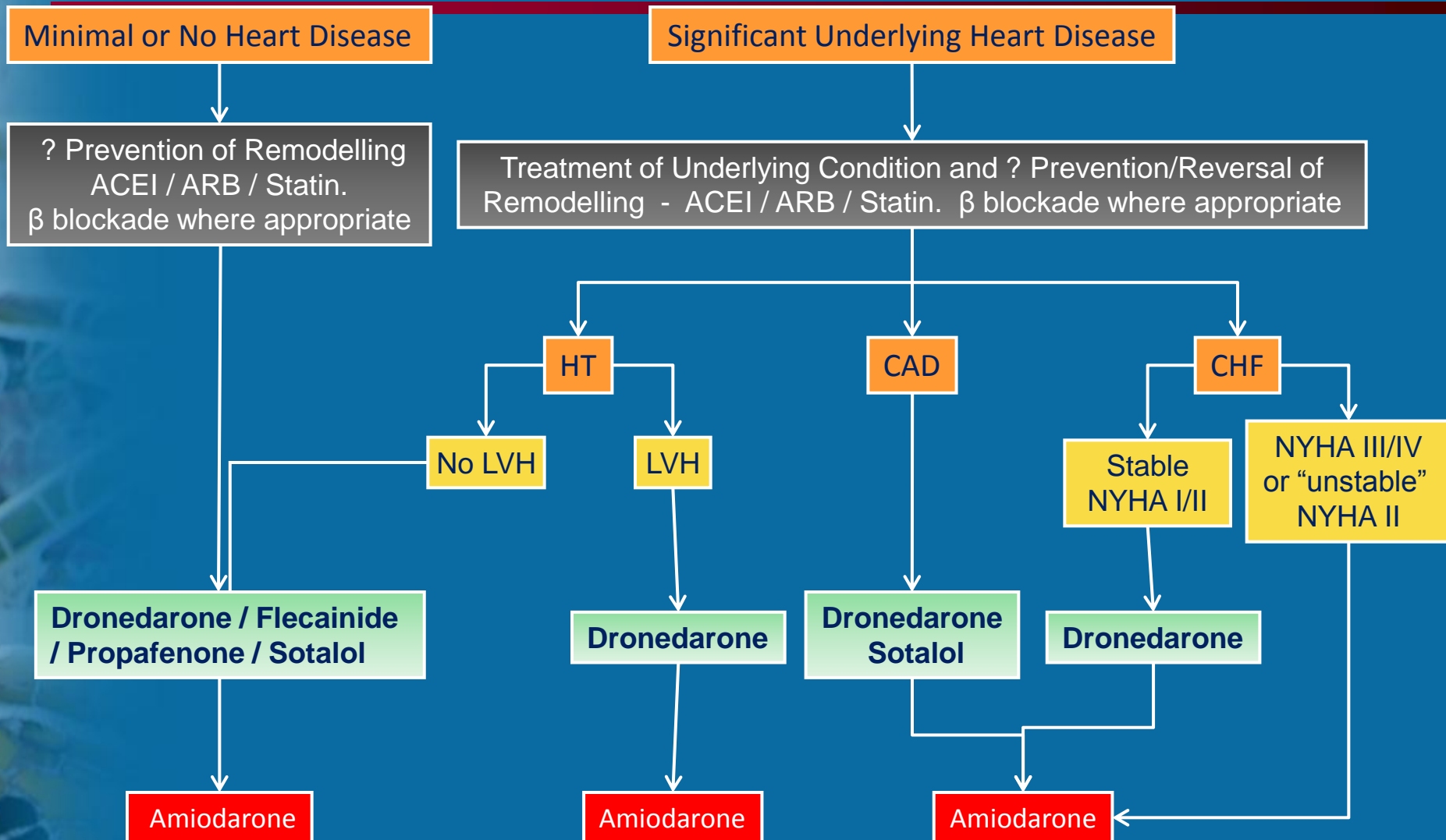


No. at Risk

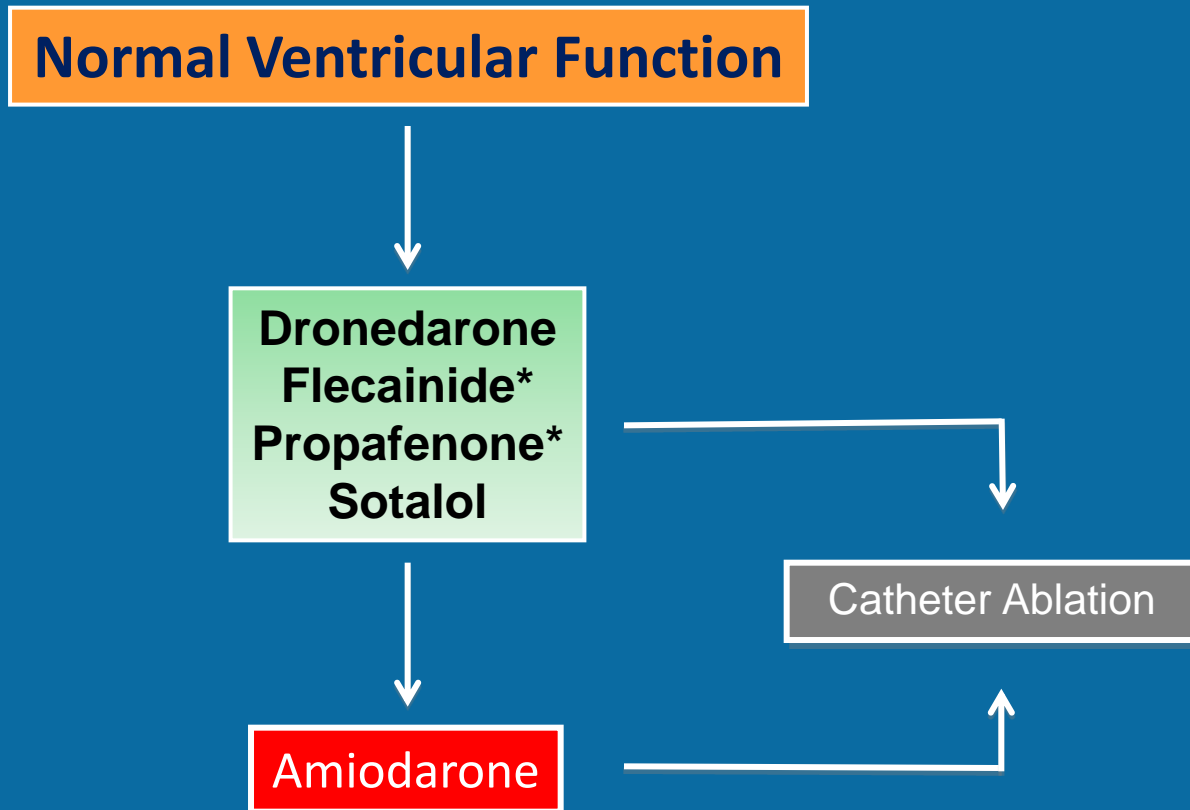
Placebo	1617	1429	882	361
Dronedarone	1619	1389	879	334

Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

Antiarrhythmic Drugs for AF Management

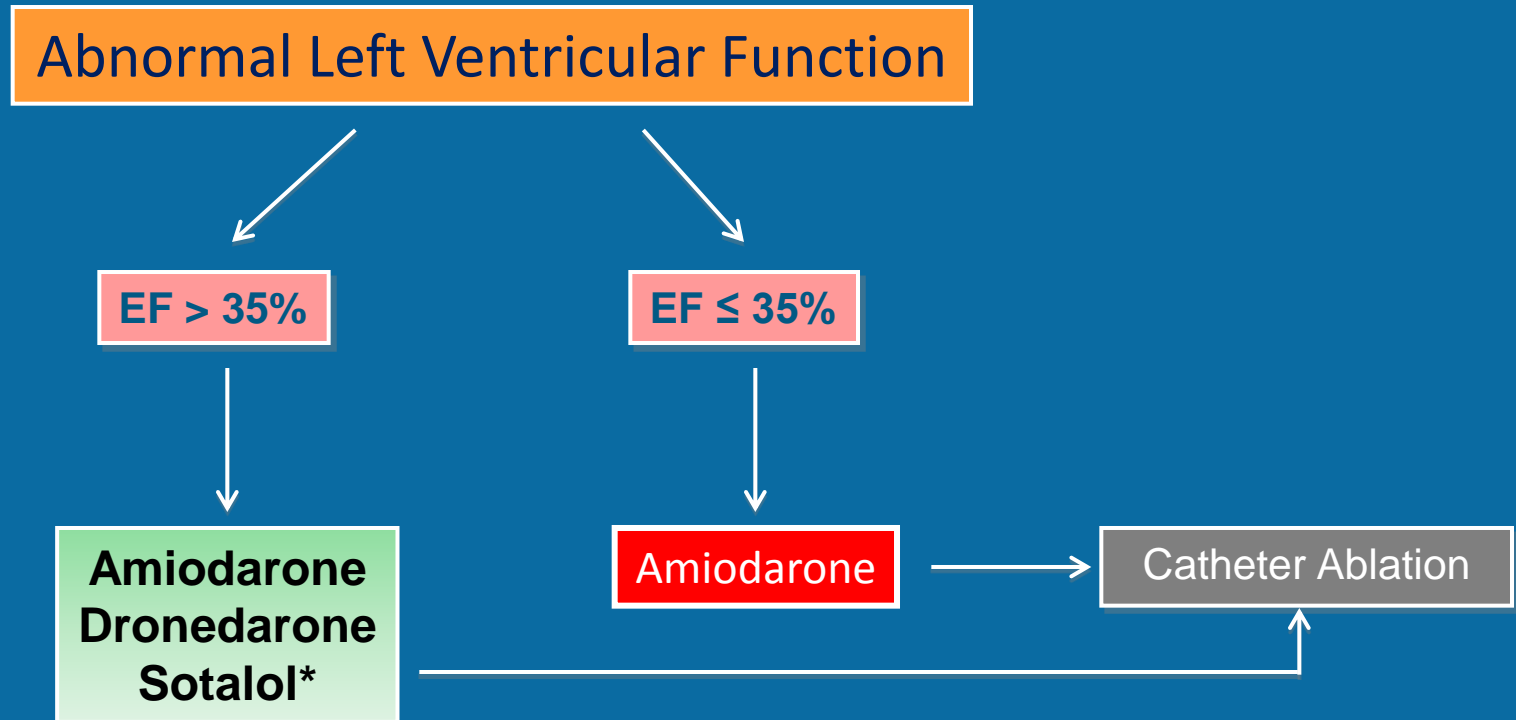


Canadian Cardiovascular Society Antiarrhythmic Drugs – Normal EF



- *Class I agents should be AVOIDED in CAD
They should be combined with an AV-nodal
blocking agents*

Canadian Cardiovascular Society Antiarrhythmic Drugs – Low EF



** Sotalol should be used with caution with EF 35-40%
Contra-indicated in women >65 years taking diuretics*

Rhythm-Control Choices Normal Systolic Function No Hx of CHF

Practical tip. Dronedaronone is a reasonable choice for rhythm control in selected patients with AF. Typically, these would be patients with nonpermanent (predominantly paroxysmal) AF with minimal structural heart disease. Consideration should be given to monitoring for liver enzyme elevations within 6 months of initiating therapy with dronedaronone.

Drugs are listed in alphabetical order

- * Dronedaronone should be used with caution in combination with digoxin
- † Class I agents should be **AVOIDED** in CAD and should be **COMBINED** with AV-nodal blocking agents
- ‡ Sotalol should be used with caution in those at risk for torsades de pointes VT (eg, female, age > 65 yr, taking diuretics)

Summary

- Dronedarone significantly prolongs time to first cardiovascular hospitalization or death in moderate to high risk elderly AF patients.
- All-cause mortality was not increased in patients receiving dronedarone.
- Cardiovascular mortality, specifically arrhythmic death, was lower in the dronedarone compared to the placebo group.
- The reduction in CV hospitalization was mainly due to fewer admissions for AF and acute coronary syndromes.
- Discontinuation of study drug was similar in both groups, indicating good tolerability of dronedarone.

Alternatives a MBE

Fundamento Decision Clinica	Marcador	Forma de Medicion	Unidad
<ul style="list-style-type: none"> Evidencia Eminencia 	RCT Brillo pelo blanco	Meta-analisis Luminometro	Razon Relativa Densidad Optica
<ul style="list-style-type: none"> Vehemencia 	Nivel de estridencia	Audiometro	Decibeles
<ul style="list-style-type: none"> Elocuencia/ Score Elegancia 	Labia/ calidad ropa	Teflometro	Adesina
<ul style="list-style-type: none"> Providencia 	Fervor religioso	Sextante mide angulo de genuflexión	UI de piedad
<ul style="list-style-type: none"> Difidencia 	Nivel depresión	Nihilometro	Suspiros/min
<ul style="list-style-type: none"> Paranoia 	Temor a ser demandado	Exámenes Todos!	Cuenta Banco
<ul style="list-style-type: none"> AutoConfianza* <p>* Exclusivo Cirujanos CV</p>	Verraquera!	Test Sudoración	Sudor/cm

Alternatives to EBM

Basis for clinical decisions	Marker	Measuring device	Unit of measurement
Evidencia	RCT	Meta-analyses	Odds ratio

Evidencia tipo SC Sentido Comun!