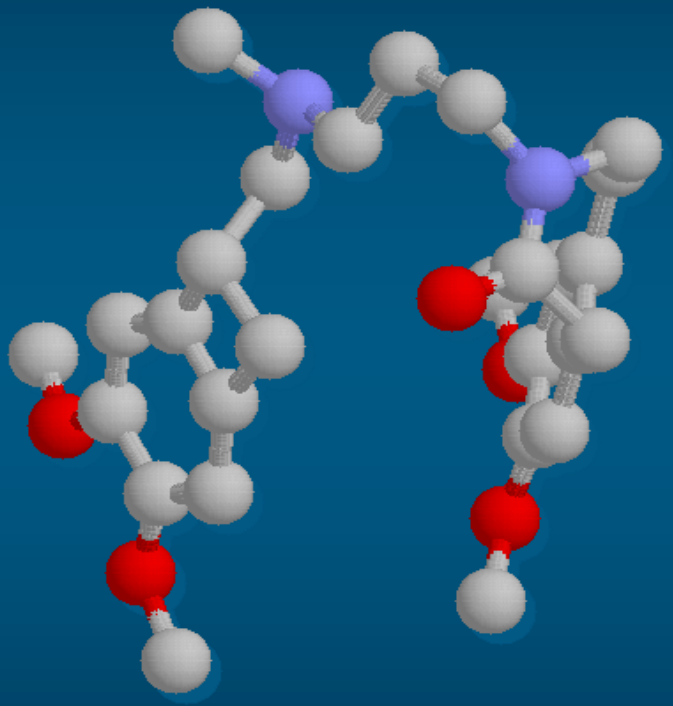
Rome Cardiology Forum

Update on Atrial Fibrillation

Rome, January 29th-31st 2014



Pharmacological Prevention of Atrial Fibrillation

John Camm

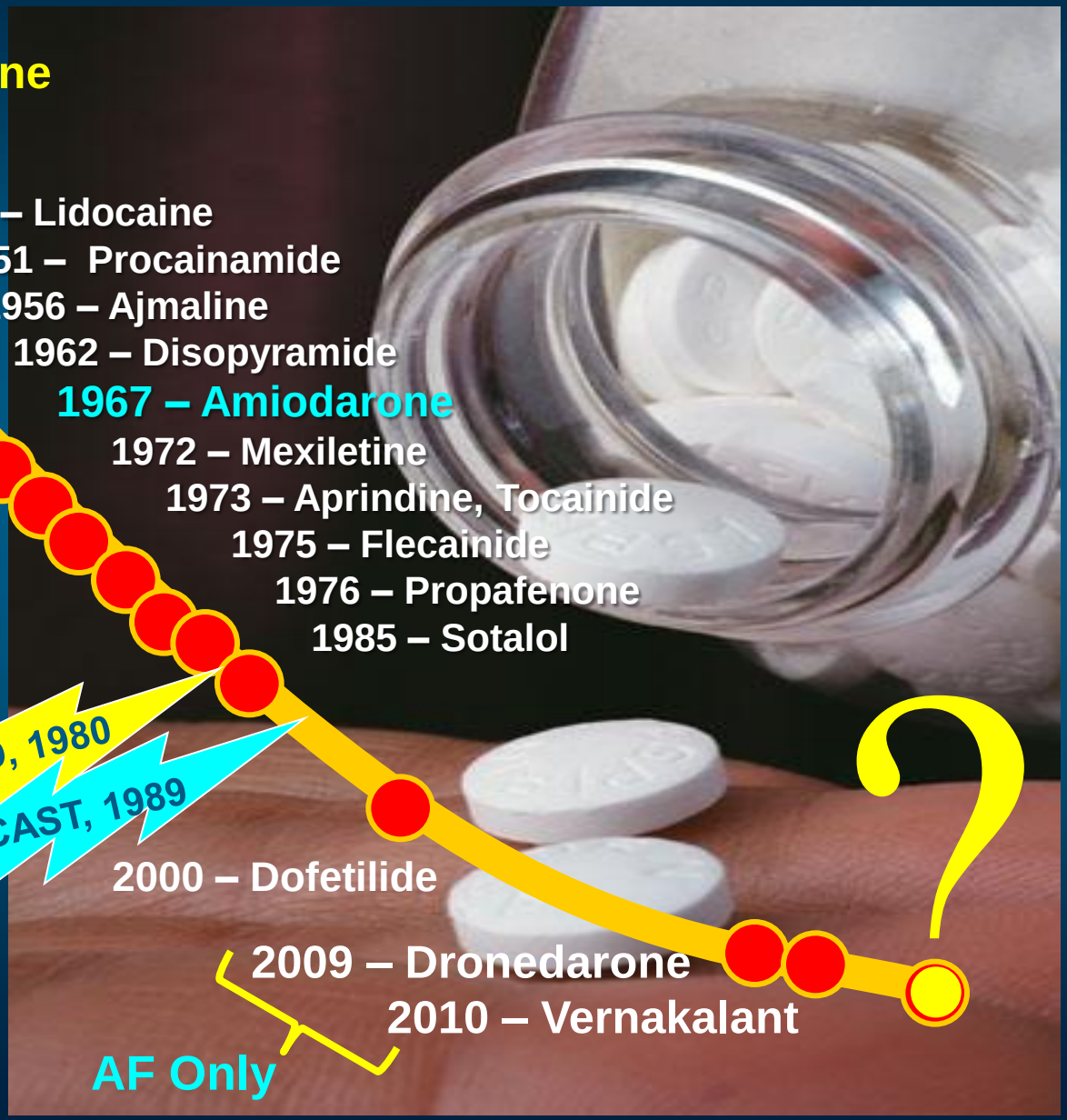
St. George's University of London, UK

St George's University of London

Conflicts of Interest: Consultant/Advisor/Speaker

Advisor / Speaker : Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

History of Antiarrhythmic Drugs



Antiarrhythmic Medical Therapies

~~Class Ia: Disopyramide~~, Quinidine and Procainamide
~~Class 1b: mexiletine, tocainide~~

Beta blocker

Antiarrhythmic Agents
New and Old

Class III
- Amiodarone
- Sotalol

Class Ic
- Propafenone
- Flecainide

New Class III Agents
- Nexterone and Budio-darone
- USA only
- ICD/VT only
- Abandoned
- Dronedarone
- Vanoxerine
- Abandoned
- Vernakalant

Multi-channel blockers

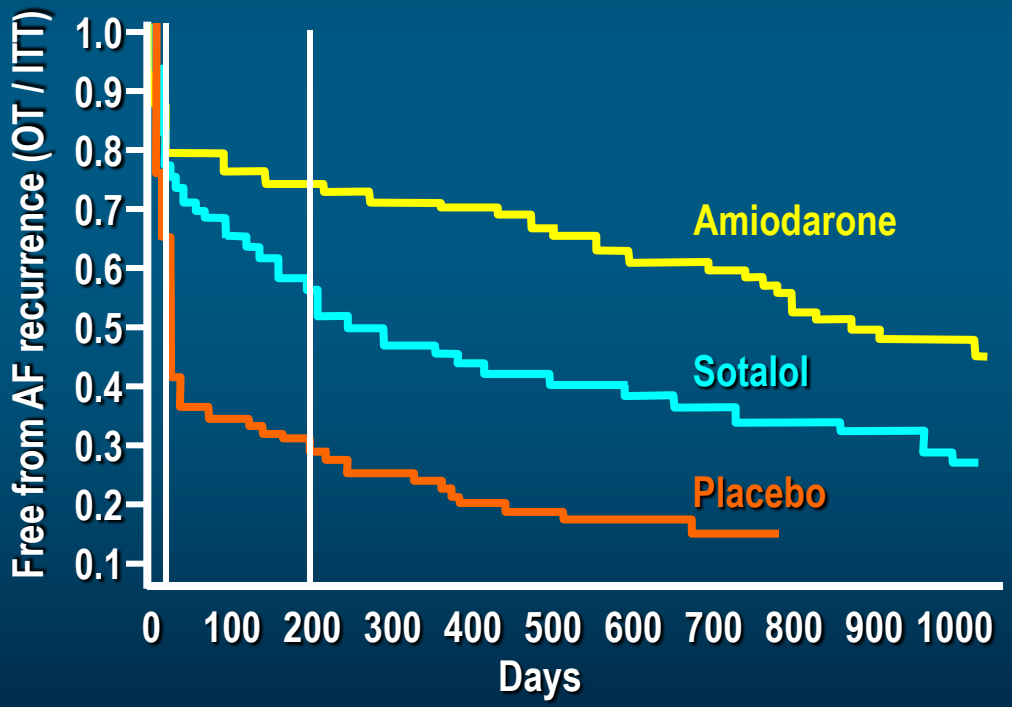
Upstream therapies

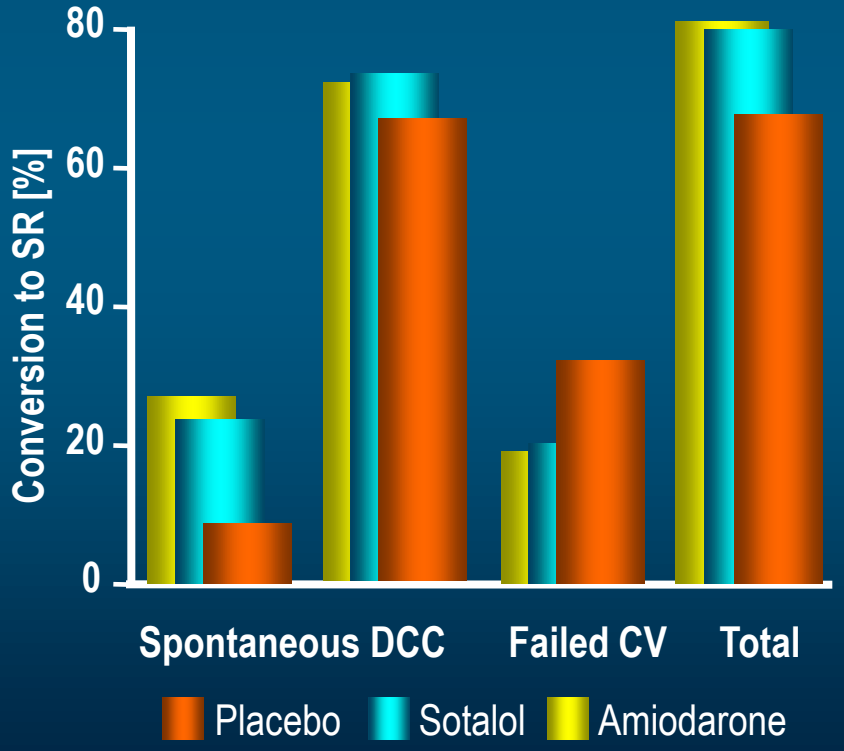
Novel Drugs
- Ryanodine Receptor Modulator
- SAC Blockers
- Rotigaptide Dangaptide
- Ranolazine
- Na+/H+ Inhibitor
- Na+/Ca2+ Inhibitor
- NTC-801
- Chloroquine
- Xen 0103
- Colchicine

Modified from Savelieva I and Camm AJ. Europace 2008:10:647–65

SAFE-T *Sotalol Amiodarone AF Efficacy Trial*

- VA Cooperative Study
- N=665, 20% AF >1 year:
- Amio 267, Sot 261, Placebo 137
- Follow-up 1year with TTM weekly
- 1º EP: time to 1st AF recn after CV

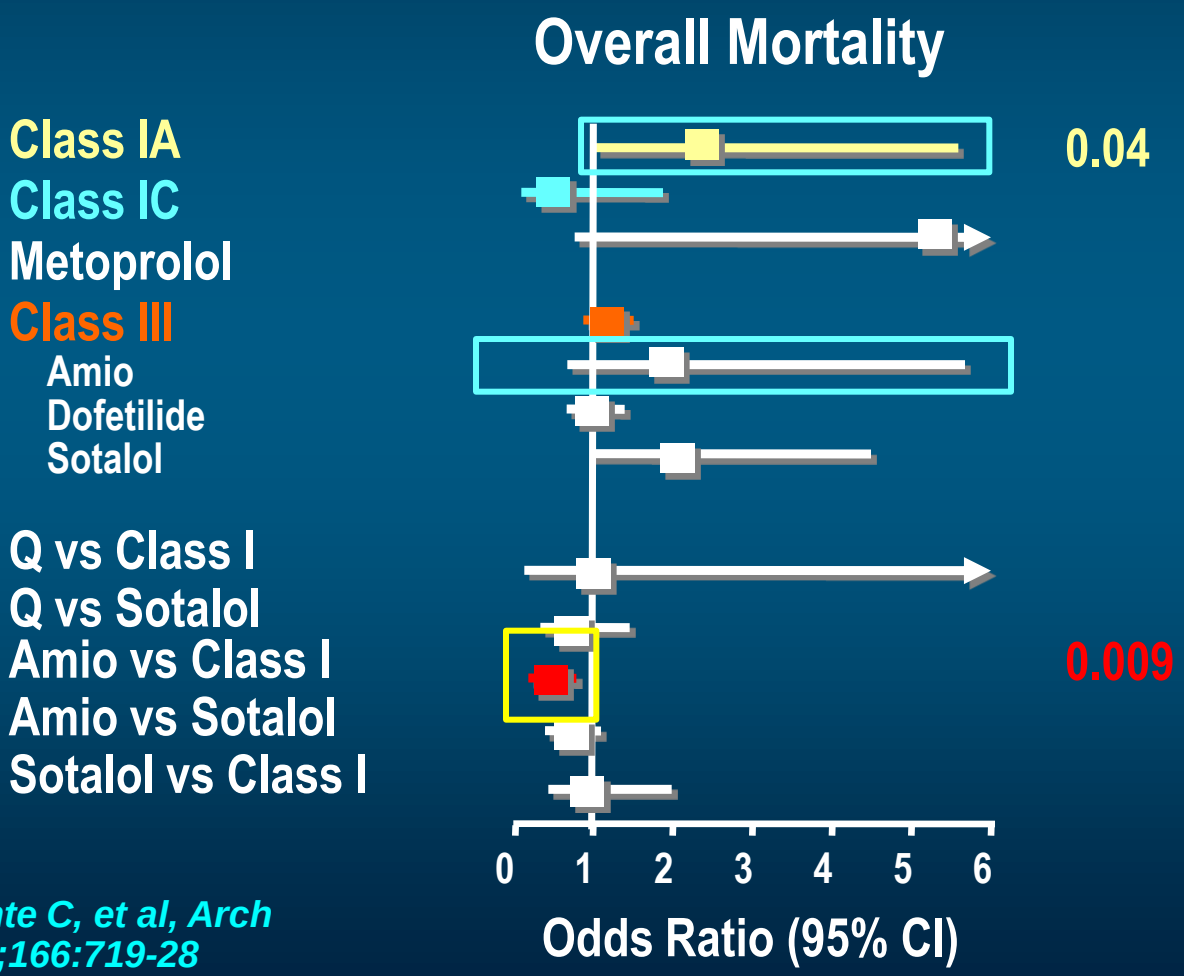




Singh BN et al. NEJM. 2005;352:1861-1872.

AADs for Mortality Reduction after DCC

Systematic Review of RCTs

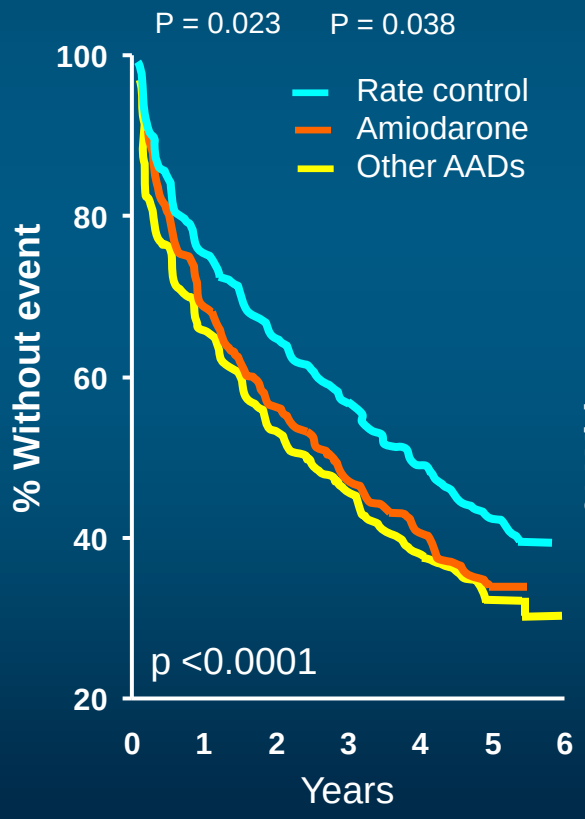


Lafuente-Lafuente C, et al, Arch Intern Med 2006;166:719-28

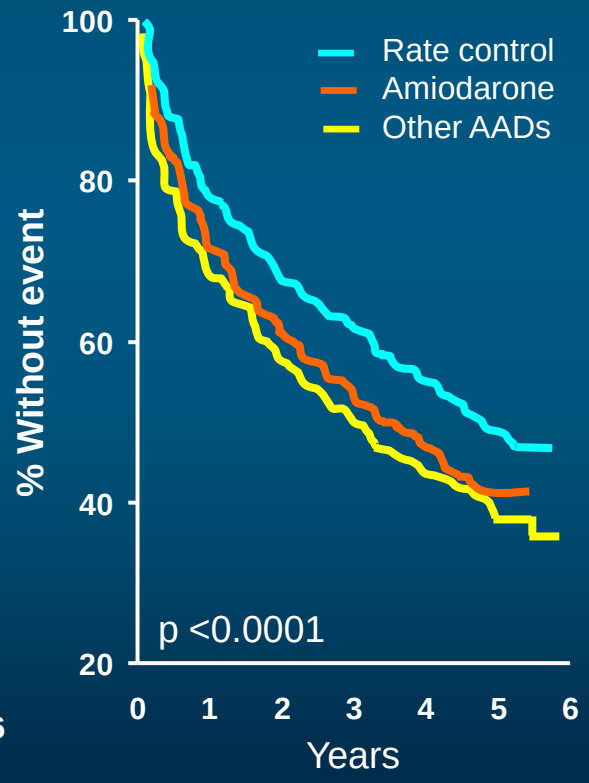
Rates of Mortality and Hospitalizations AFFIRM Study by Treatment Group

AFFIRM	Rate n= 2027	Amio N =735	Other AADs n=1298
Age, yrs	69.6	69.9	69.2
Men, %	59.4	67.3	59.1
CAD,%	37.3	46.0	35.1
CMP,%	8.6	12.7	5.7
CHF,%	23.4	30.1	18.7

Composite endpoint (ACM + CVH)



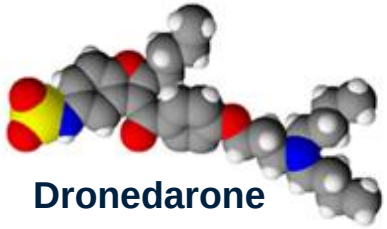
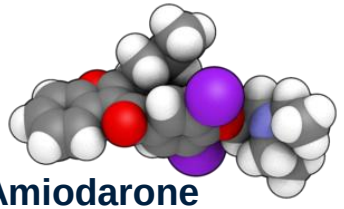
CV hospitalization



Saksena S, et al. Abstracts, ACC 2010

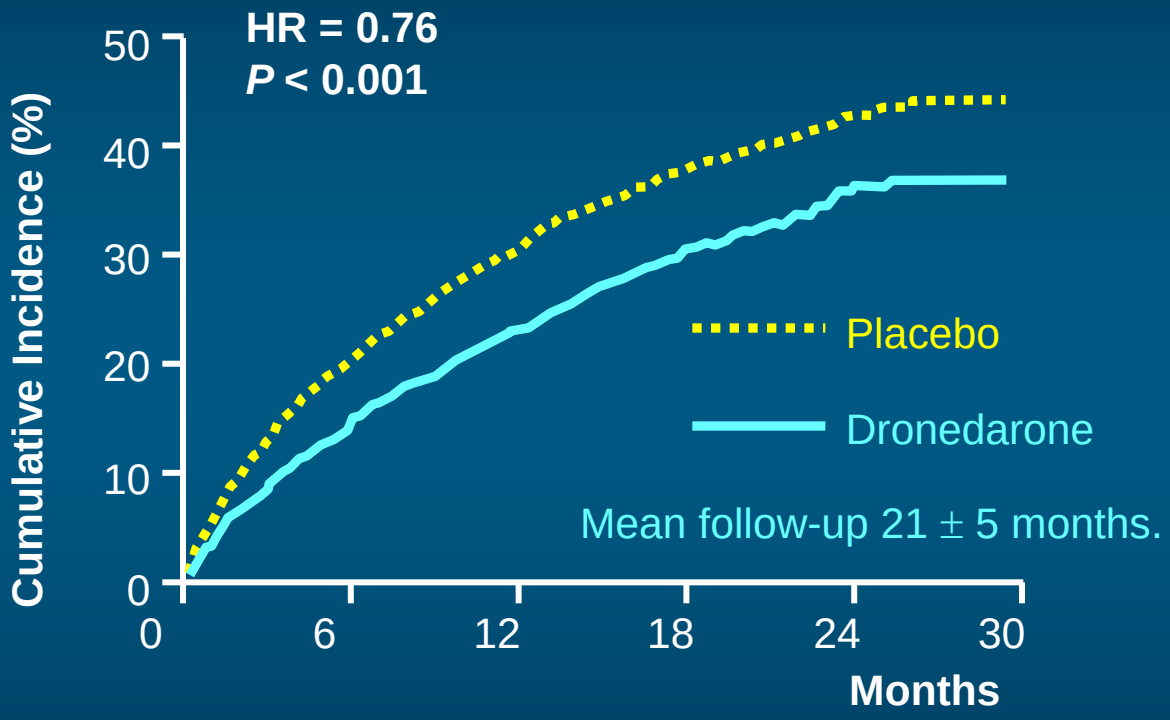
Dronedarone and Amiodarone

Main Ion Channel/Receptor Effects

Outward currents	Dronedarone	Amiodarone
I_{Kr} **(ventricle)** Guinea pig (IC_{50}; μM)	2–3	10
I_{Ks} **(ventricle)** Guinea pig (IC_{50}; μM)	10	30
I_{K1} **(ventricle)** Guinea pig (IC_{50}; μM)	>30	<30
$I_{K(Ach)}$ **(atrium)** Guinea pig (IC_{50}; μM)	0.01	1
Inward currents	 Dronedarone	 Amiodarone
I_{Na} (human; 3 μM)	97% block	41% block
$I_{Ca(L)}$ (Guinea pig; 10 μM)	76% block	85% block
Beta blockade (IC_{50}; μM)	1.8	8.7

ATHENA: Primary Outcome

Time to first cardiovascular hospitalization or death

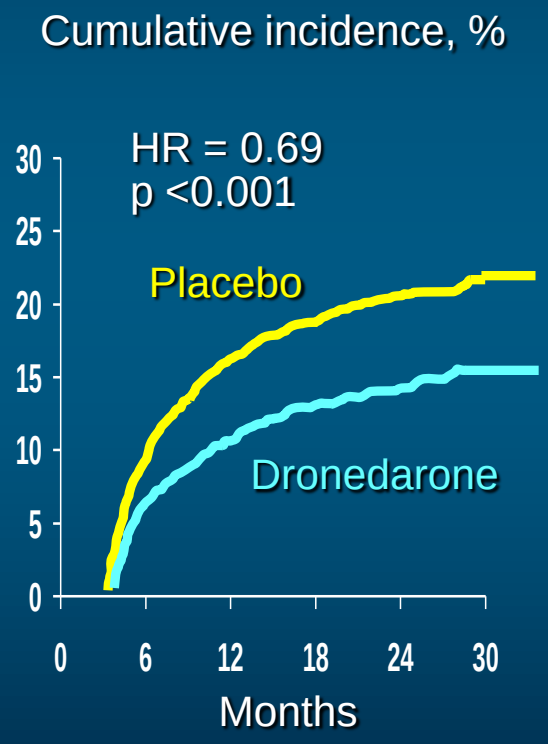


Patients at risk						
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

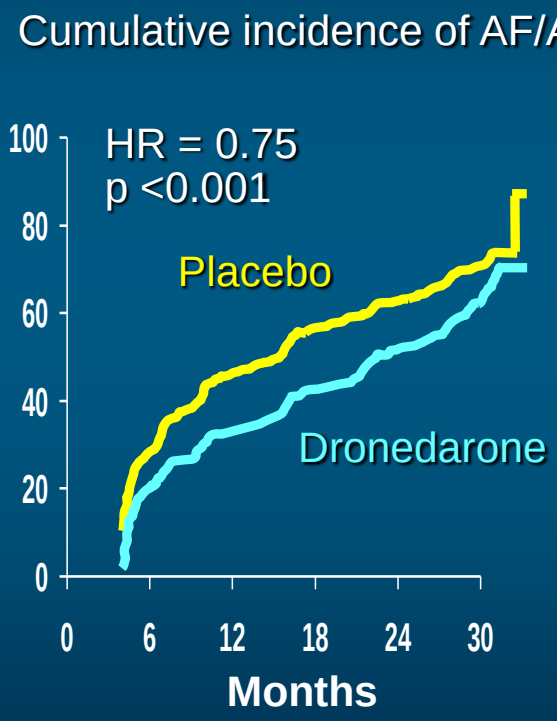
Hohnloser SH et al. ATHENA Investigators. N Engl J Med. 2009 Feb 12;360(7):668-78.

Dronedarone as an Antiarrhythmic
Examples from ATHENA

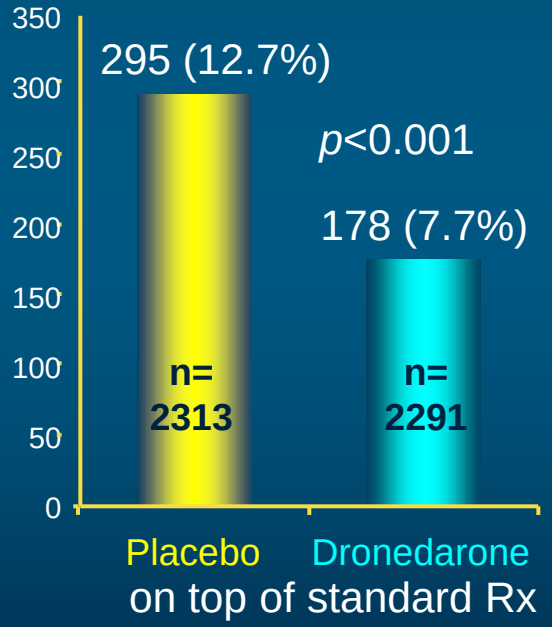
Time to 1st DCV



Time to 1st AF/AFL



No. in Permanent AF

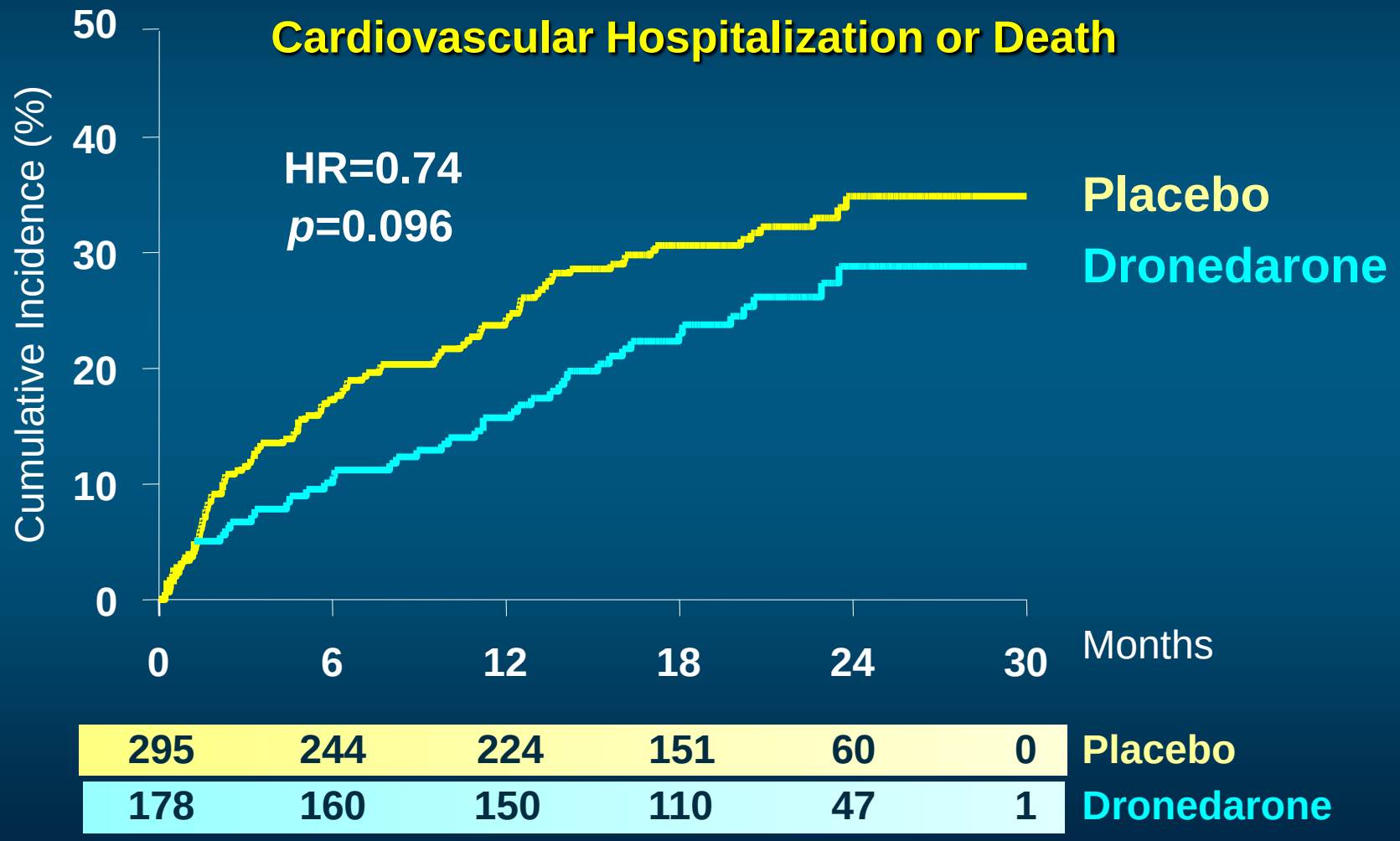


All AF related hospitalization: HR=0.626, 95% CI = [0.54; 0.73]
First AF related hospitalization: HR=0.63, 95% CI = [0.55; 0.72]

Page R, et al. Am J Cardiol 2011

Was Antiarrhythmic Effect Important?

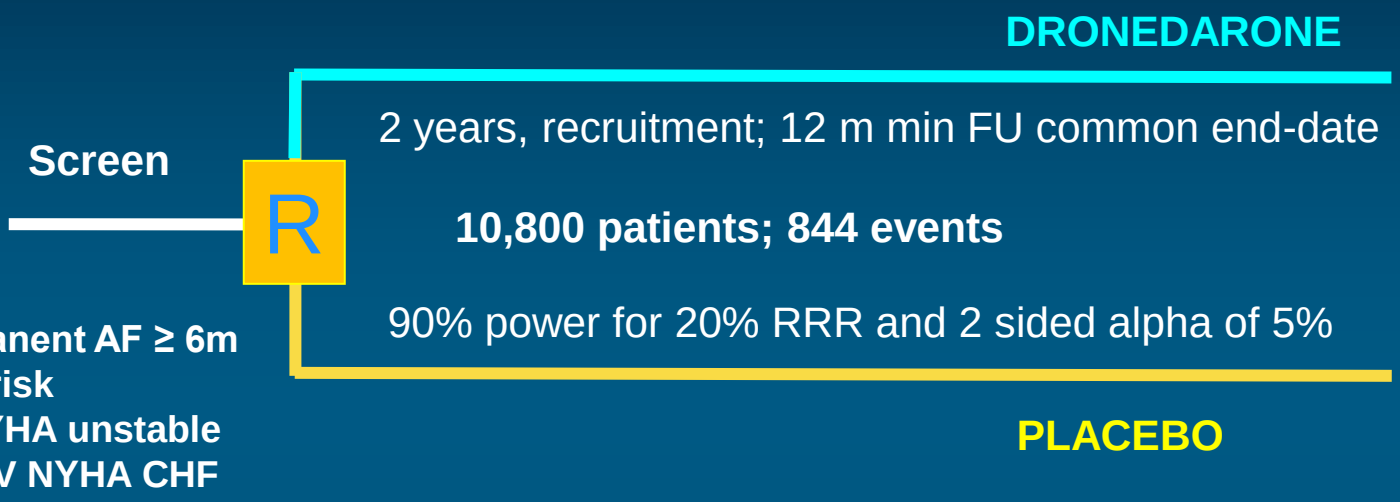
Permanent AF Patients



Mean follow-up 21 ± 5 months - on Study

PALLAS

Permanent Atrial fibriLLAtion outcome Study



1⁰ Outcomes	Dronedarone (n = 1619)		Placebo (n = 1617)		Dronedarone vs Placebo		
	Events	%/yr	Events	%/yr	HR	95% CI	P value
1st Co-primary (Stroke/MI/SEE/CV Death)	43	8.2	19	3.6	2.29	1.34-3.94	0.002
2nd Co-primary (All Death/Unplanned CV Hospitalization)	127	25.3	67	12.9	1.95	1.45-2.62	<0.001

Connolly S. et al. N Engl J Med. 2011 Nov 14. [Epub ahead of print]

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 ≤ 40%	4.2	4.7	21.3	20.7
Peripheral Arterial Disease	-	-	11.6	13.2
Age ≥ 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

Sub-groups – 2nd Co-Primary Outcome

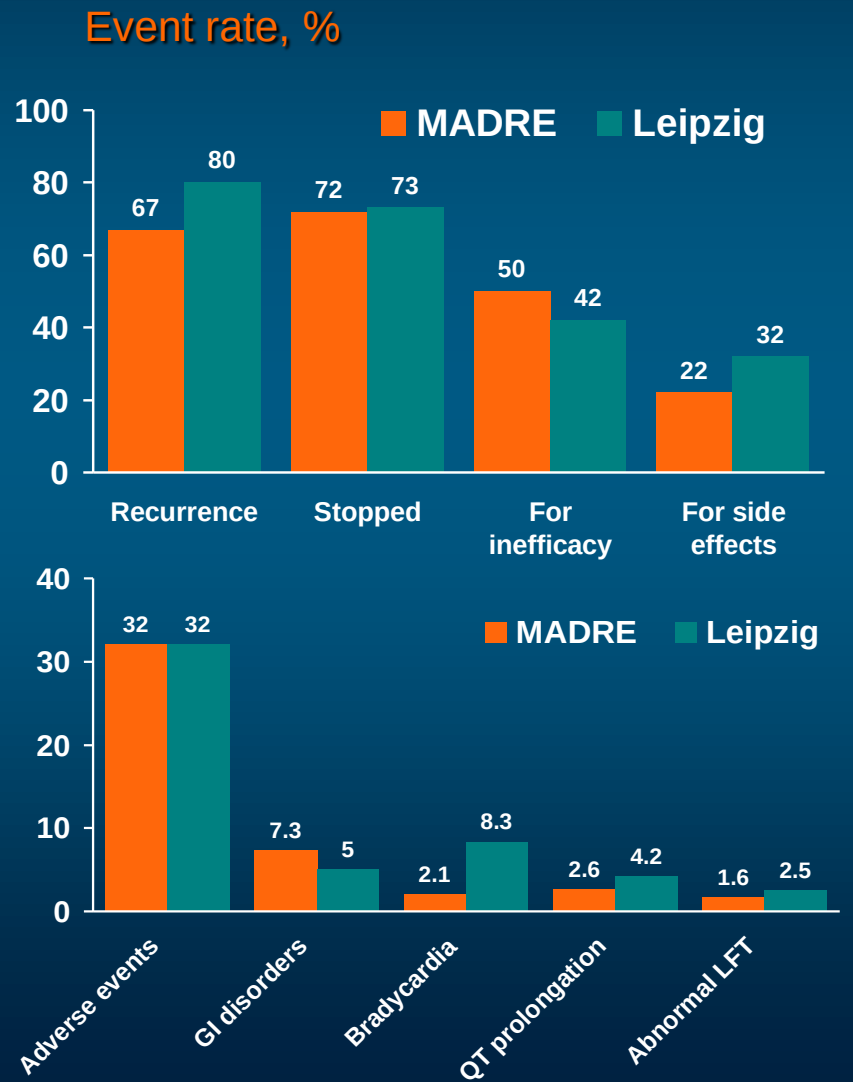
Characteristics	N	HR [95% CI] [a]	Hazard Ration (95% CI)	P value [b]
Overall		1.95 [1.45;2.62]		
Age				
<75	1562	2.24 [1.42;3.52]		0.423
≥75	1674	2.75 [1.19;2.59]		
Duration of perm. AF				
6 months to 2 years	988	1.91 [1.20;3.04]		0.945
>2 years	2243	1.94 [1.32;2.85]		
Baseline LVEF			LVEF	
LVEF≤40%	680	2.17 [1.15;4.07]		0.717
LVEF>40%	2556	1.89 [1.35;2.64]		
NYHA			NYHA	
No class II/III	1490	2.03 [1.23;3.36]		0.842
Class II/III	1746	1.91 [1.32;2.75]		
CHADS				
CHADS ≤2	1326	1.92 [1.16;3.19]		0.933
CHADS >2	1908	1.96 [1.36;2.82]		
Stroke or TIA history				
N	2342	2.12 [1.49;3.01]		0.353
Y	894	1.55 [0.88;2.72]		
Coronary artery disease				
N	1908	1.87 [1.23;2.84]		0.834
Y	1327	1.98 [1.30;3.01]		
Baseline HR			HR	
HR <65 bpm	644	3.65 [1.75;7.59]		0.057
HR ≥65 bpm	2591	1.67 [1.20;2.32]		
Baseline SBP				
SBP <130 mmHg	1468	1.84 [1.19;2.83]		0.805
SBP ≥130 mmHg	1708	1.97 [1.30;2.98]		
Digoxin				
N	2166	2.07 [1.44;2.97]		0.554
Y	1070	1.70 [1.02;2.83]		
Beta blocking agents				
N	834	1.62 [0.97;2.71]		0.377
Y	2402	2.13 [1.48;3.07]		
Vitamin K antagonist or Dabigatran				
N	447	1.31 [0.71;2.42]		0.099
Y	2789	2.23 [1.59;3.14]		
Regions				
North America/Western Europe	1512	2.28 [1.48;3.51]		0.300
Other regions	1724	1.67 [1.11;2.51]		

a: Determined from Cox regression model

Connolly S. et al. N Engl J Med 2011;365:2268-76

Post-market Experience: Magdeburg and Leipzig Registries

Registry	Magdeburg (MADRE)	Leipzig
# patients	191	120
Age, yrs	63 ± 10	67 ± 9
PAF, %	63	34
Duration, yrs	3.6 ± 4.1	6.1± 6.8
HTN, %	66	93
CAD, %	22	17
Prior AAD, %	63	19
Prior PVI	0	28
Follow-up, mos	14.3 ± 4.9	6-9



More effective in non-lone AF (62% vs 84%), U-shape relationship with LA size

Said SM, et al. Int J Cardiol 2013;167:2600-4
Said SM, et al. JCP 2013;53:841-5

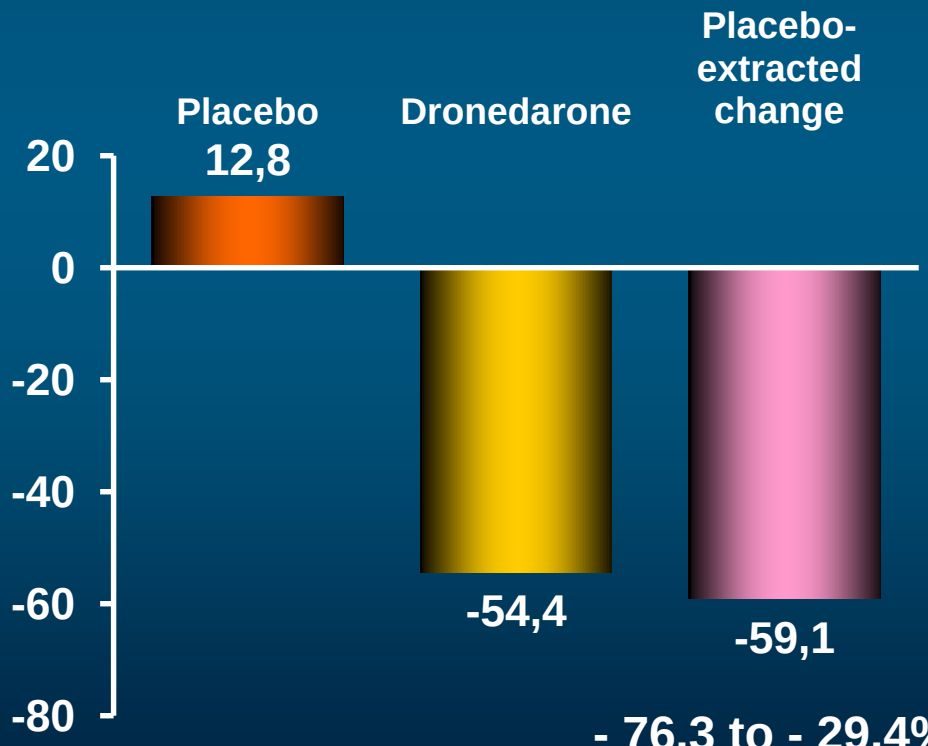
Dronedarone in PAF: HESTIA


The virgin goddess of the hearth and the home

A placebo-controlled, double-blind, randomized, multi-center study to assess the effects of Dronedarone 400 mg BID for 12 weeks on atrial fibrillation (AF) burden in subjects with permanent pacemakers

- Patients with PAF and DDD PM
- Planned n = 290,
  Enrolled n = 112
- AF burden at baseline Placebo vs Dronedarone: 16% vs 21%
- Duration: 4 weeks baseline,
  12 weeks therapy

1º EP: changes in AF burden from baseline at 12 weeks, %



At 12 weeks: 23 vs 18%

- 76.3 to - 29.4%
p=0.0015

Department of Defence Database Overview

Death from Any Cause

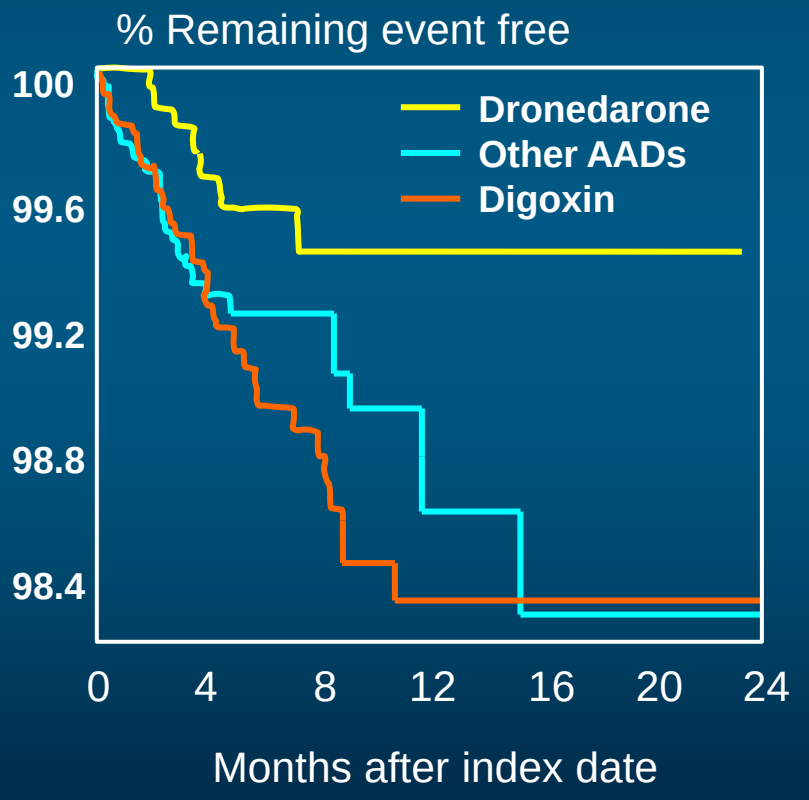
Propensity-score matching of 2079 patients on dronedarone and 4158 patients on "other AADs", and 4158 on digoxin

Overall Results

	Dronedarone N=2079	Other AADs N=4158	Digoxin N=4158
Number of event	7	30	36
Percentages p-value(1)	0.34% Ref	0.73% 0.079	0.87% 0.022
Event-Rate / 10,000 PM p-value	5.16 Ref	12.11 0.044	13.48 0.014
HR (95%CI) P-value	Ref	2.28 (1.00 – 5.20) 0.049	2.64 (1.18 – 5.94) 0.019

- All-cause mortality was significantly higher in the "other AADs (p= 0.049) and digoxin (p= 0.019)

Kaplan-Meier Curves

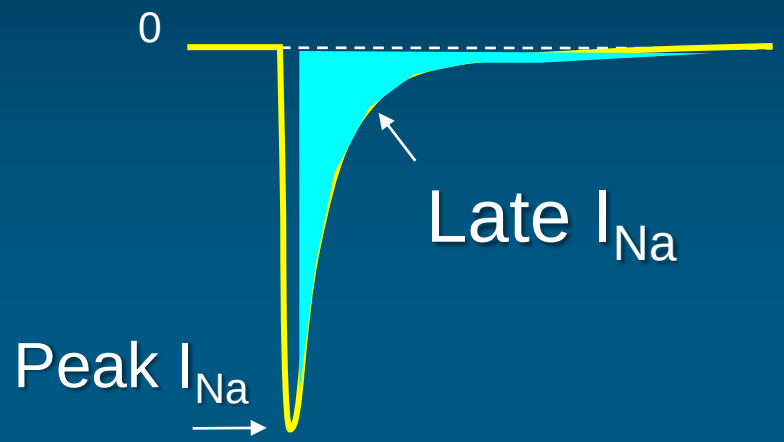


Hazard ratio [HR] (Other AADs vs Dronedarone = 2.28; CI:1.00 to 5.20; *P* <.05])

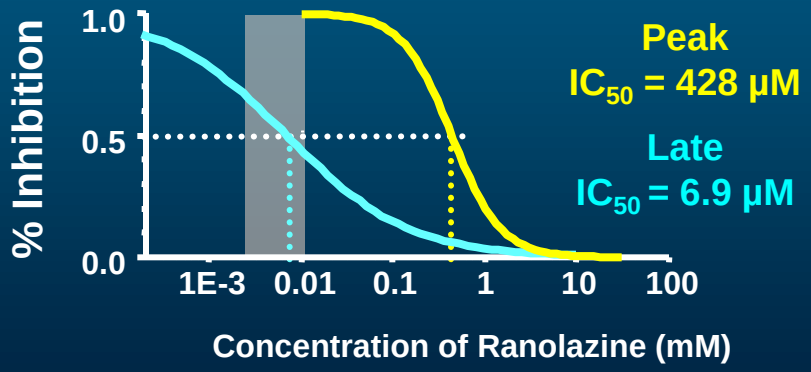
Goehring E, et al. 2013 ACC San Francisco

Ranolazine

Sodium Current

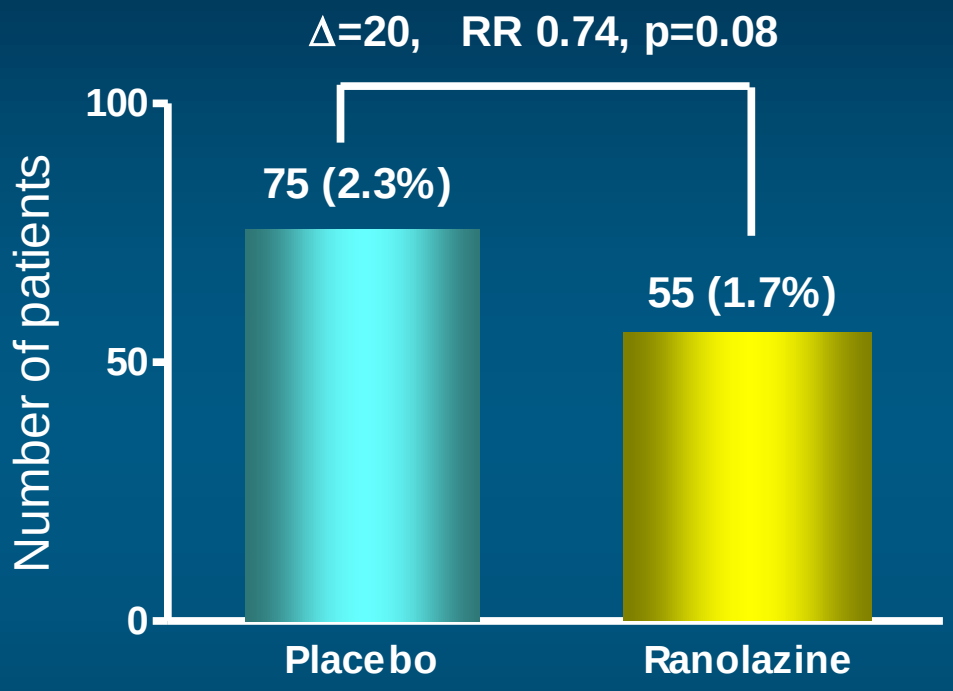


Human Cardiac NaCh in HEK293 Cells



Rajamani S., et al., Eur Heart J. 28(1) 2007

New-Onset Atrial Fibrillation



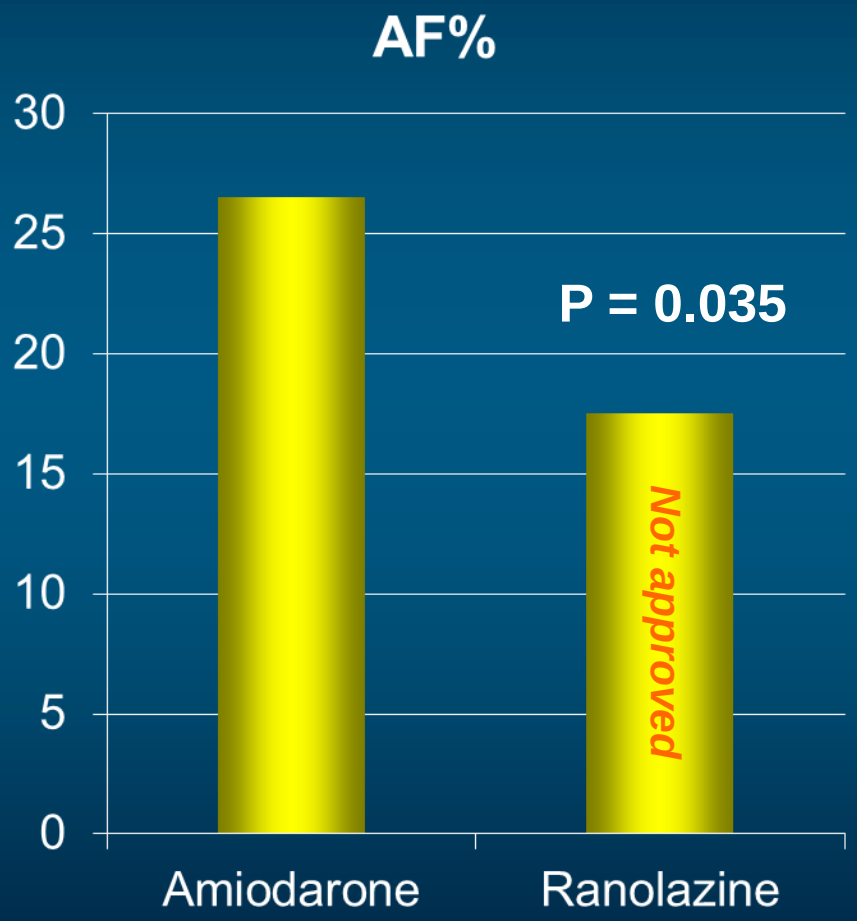
MERLIN TIMI 36

TIMI

Scirica et al. Circulation. 2007;116:1449-1457.

Ranolazine versus Amiodarone
AF Prophylaxis After CABG

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10–14 days) - N=211 (53.7%)
- Ranolazine (1,500 mg preoperative followed by 1,000 mg twice daily for 10–14 days) - N=182 (46.3%)
- Mean age 65 ± 10 years, 72% male



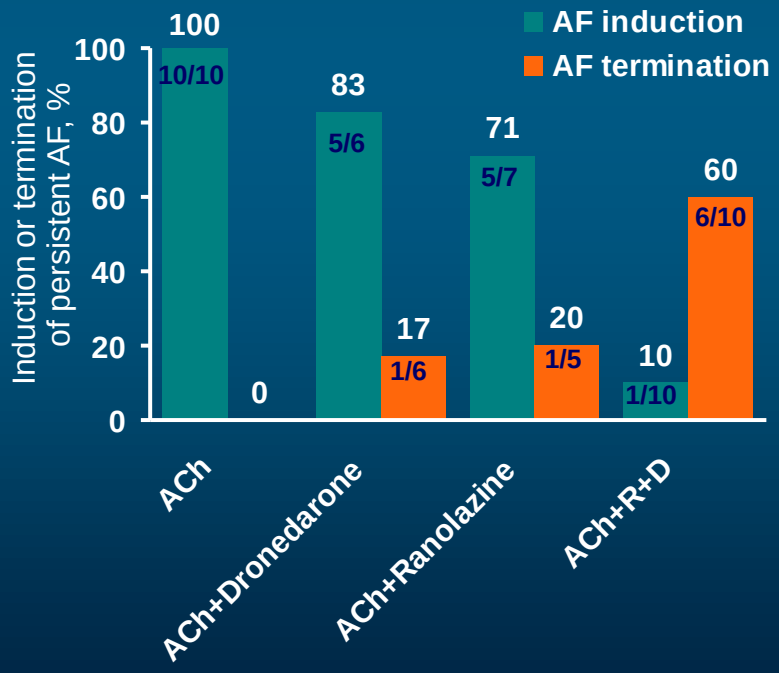
Ranolazine associated independently with a reduction of post-op AF

CABG=coronary artery bypass grafting

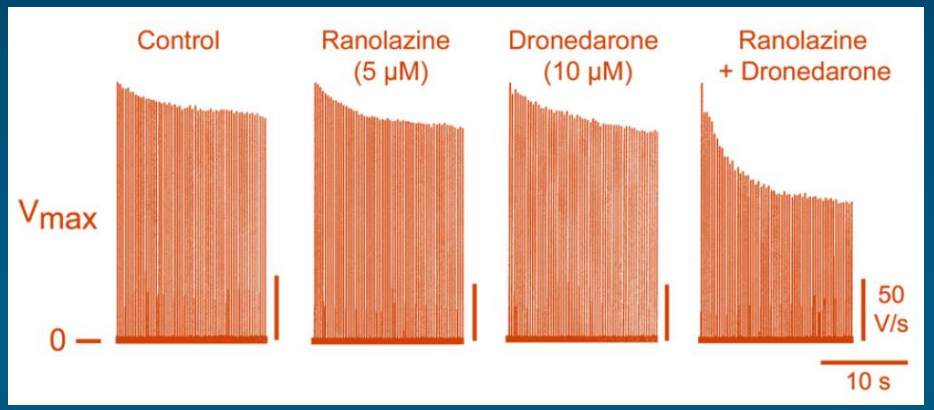
Murdock D, et al. ACC Abstracts 2011, New Orleans, LA, USA

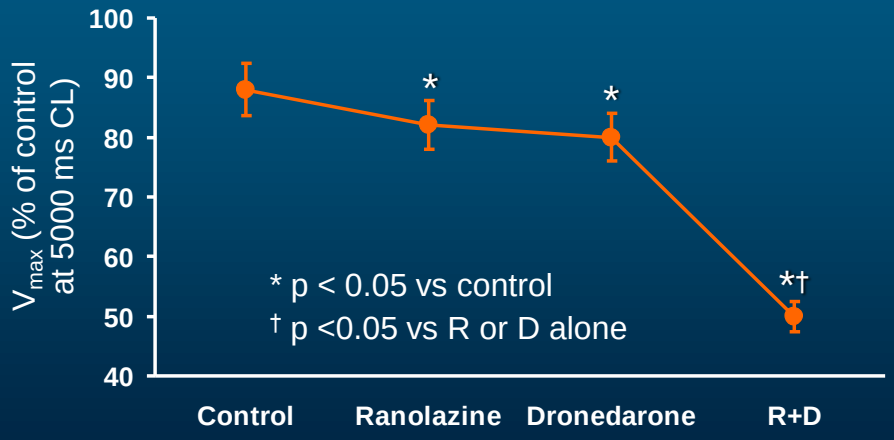
Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 μmol/L
- Dronedarone 10 μmol/L



Pulmonary vein preparations





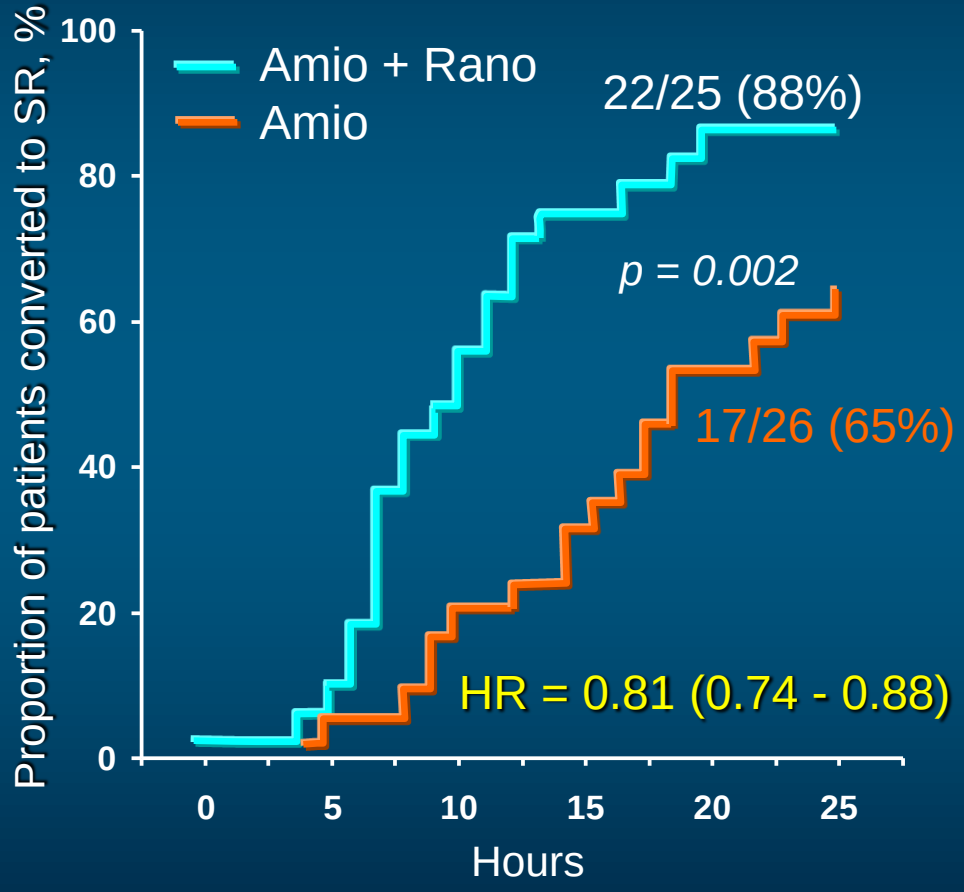
Burashnikov A, et al. J Am Coll Cardiol 2010;56:1216–24

Pharmacological Cardioversion of AF

Combination of Amiodarone and Ranolazine

Not approved

- Pilot RCT
- N = 51 with AF < 48 h
- Age 63 ± 8 years, 65% men
- HTN 68–77%, CAD 20–27%
- I.V. amio 5 mg/kg for 1 h followed by infusion of 50 mg/h for 24 h
- I.V. amio + ranolazine 1,500 mg p.o.
- 1º EP: conversion within 24 h

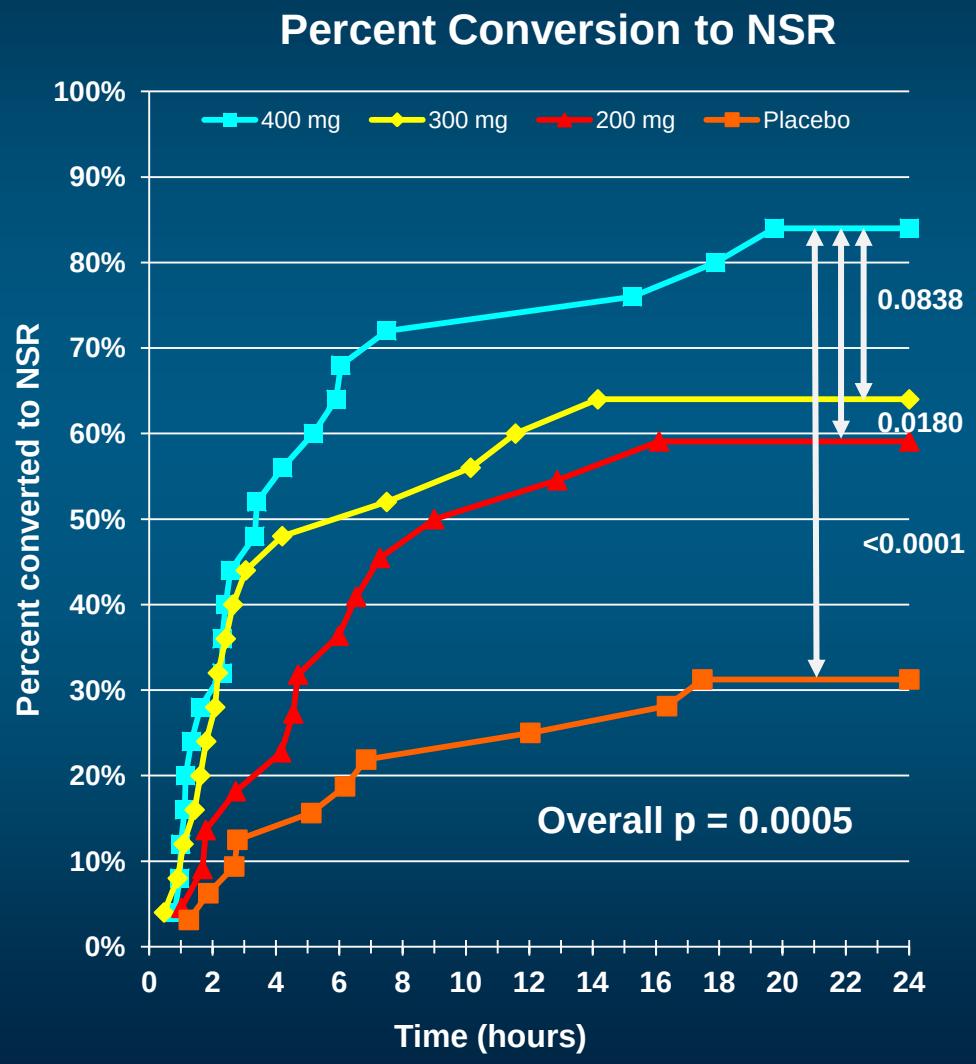


Median time to conversion:
18 h (Amio) vs 10 h (Amio+Rano)

SR=sinus rhythm

Fragakis N, et al. Am J Cardiol 2012;110:673–7

Vanoxerine and Pharmacologic AF CV
The COR-ART Study



Dittrich H, et al. AHA Poster Dallas 2013

- Vanoxerine: potent blocker of IKr (hERG) channel and Na and L-type Ca channel blocker
- Extensive safety experience as anti Parkinson Syndrome drug

Subjects who have been in symptomatic AF/AFL for 3 hours to <7 days

Randomized, Double-Blind, Placebo-Controlled, Dose-Modifying

- Placebo - 30 patients
- 200 mg - 25 patients
- 300 mg - 25 patients
- 400 mg - 25 patients

- No VT adverse event
- 1 sinus pause (3s) at 200 mg
- 3 QT prolongation at 400 mg

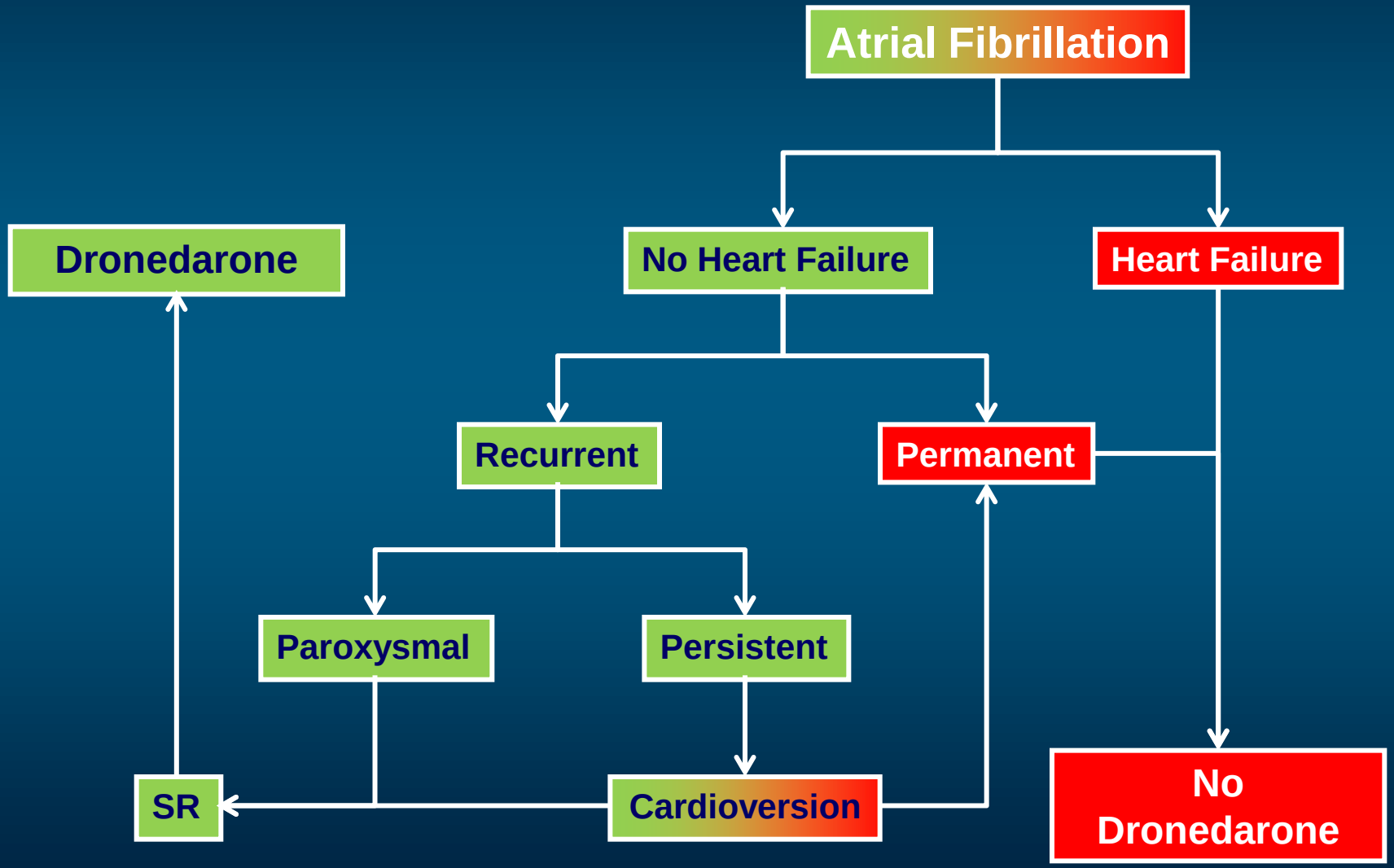
Conclusions

- Amiodarone is the best AAD drug to suppress recurrences of AF, but does not reduce mortality or hospitalisation
- Dronedarone reduces CV hospitalisations and ? CV mortality in patients with recurrent forms of AF
- Dronedarone should not be used in patients with permanent AF, or moderate or severe heart failure/LV dysfunction
- There have been promising reports on the antiarrhythmic potential of ranolazine, but definitive studies are awaited
- The development of many potential antiarrhythmic agents has been suspended others continue to be developed

Thank you for your attention

St George's
University of London

When Use Dronedarone



Camm J, et al. Heart 2013;99:1476-80

RAFFAELLO: Ranolazine in Atrial Fibrillation Following An ELectricaL cardiOversion

- Phase IIb
- ~ 40 centres in Europe (Germany, Italy, Spain, UK)
- Planned DCC off AADs; SR maintained for 2 h
- Ranolazine: 375, 500, 750 mg bd or Placebo
- Treatment duration: 16 weeks or until documented AF recurrence in need of medical intervention
- Recruitment completed (n = 260), database locked

Clinical Trial RANO+DRONE Combination: HARMONY

- PAF with pacemakers
- N = 150, 45 centres
- Follow-up: 12 weeks
- Primary endpoint: reduction in AF burden
- Secondary endpoints: AF burden at each clinic visit at 4, 8, 12 weeks and the number of AF episodes
- Expected March 2014

NCT01522651