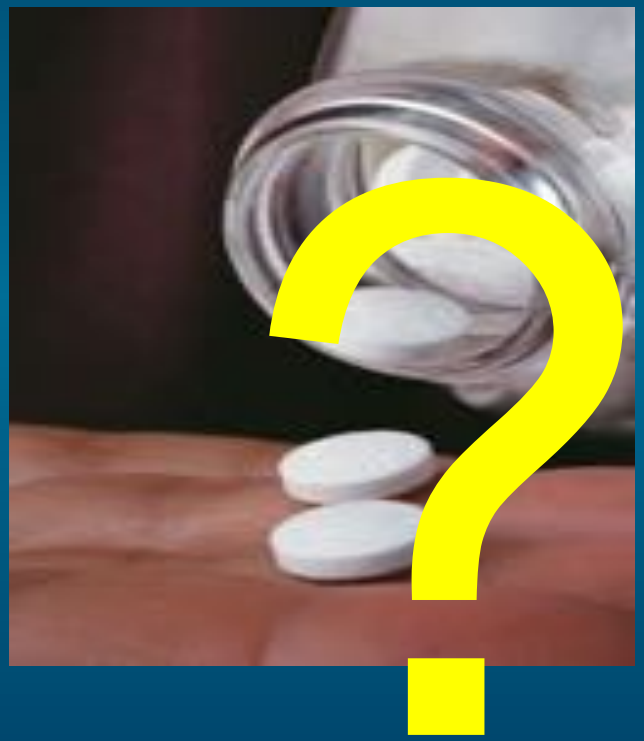
Venice Arrhythmias

16th October, 2015 - Venice

Drug Propylaxis of AF: 2015 Update



Ranolazine Alone or in Combination with Other Antiarrhythmic Drugs for Atrial Fibrillation

John Camm

St. George's University of London, UK

St George's University of London

Declaration of Interests

Chairman: NICE Guidelines on AF, 2006; ESC Guidelines on Atrial Fibrillation ,2010 and Update, 2012; ACC/AHA/ESC Guidelines on VAs and SCD; 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on heart failure, 2008; NICE Guidelines on Atrial Fibrillation, 2006; ESC VA and SCD Guidelines, 2015

Steering Committees: multiple trials including novel anticoagulants

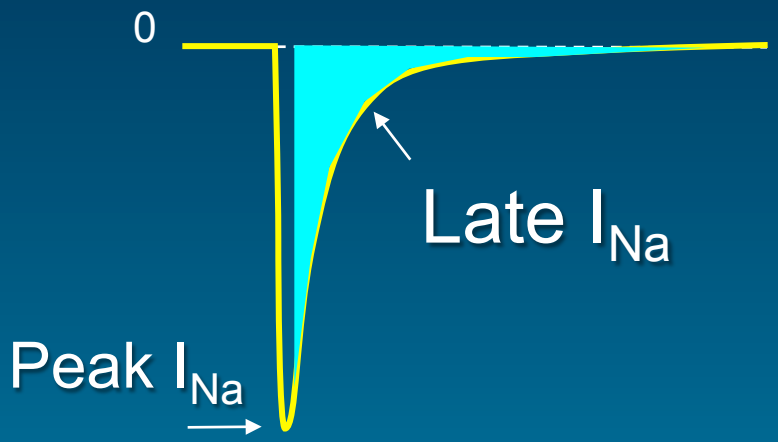
DSMBs: multiple trials including BEAUTIFUL, SHIFT, SIGNIGY, AVERROES, CASTLE-AF, ASTAR II, INOVATE, and others

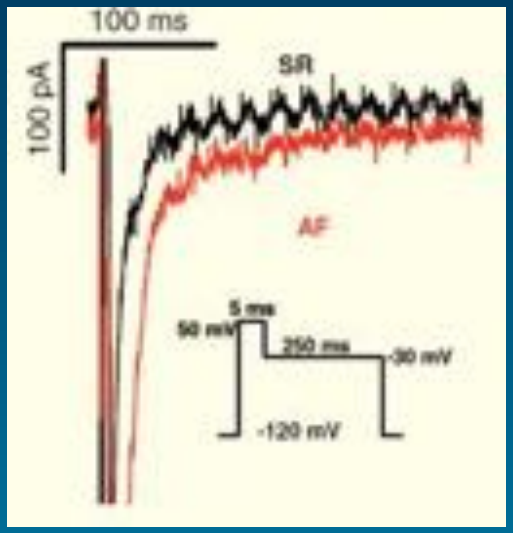
Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects

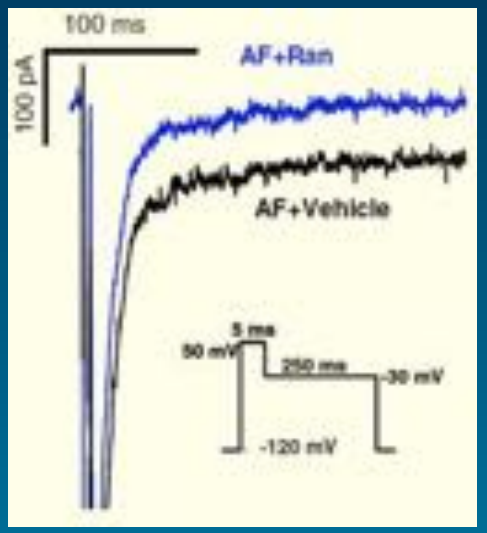
Editorial Role: Editor-in-Chief, EP-Europace and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

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

Antiarrhythmic Effects of Ranolazine



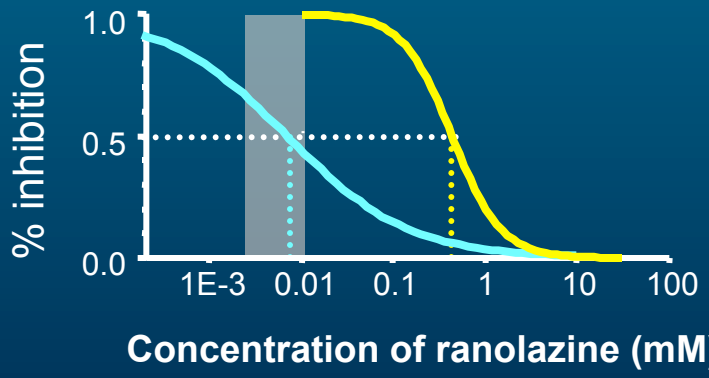




Not approved anywhere for AF

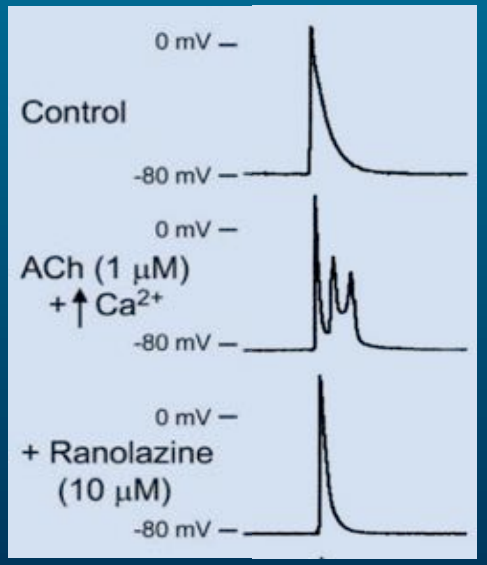
Peak: IC_{50} = 428 µM

Late: IC_{50} = 6.9 µM



- ↑ late Na^+ during AF
- ↑ intracellular Na^+
- Reversal Na^+/Ca^{2+} Ex
- ↑ intracellular Ca^{2+}

- ↑ EADs
- ↑ DADs
- ↑ spontaneous PV automaticity

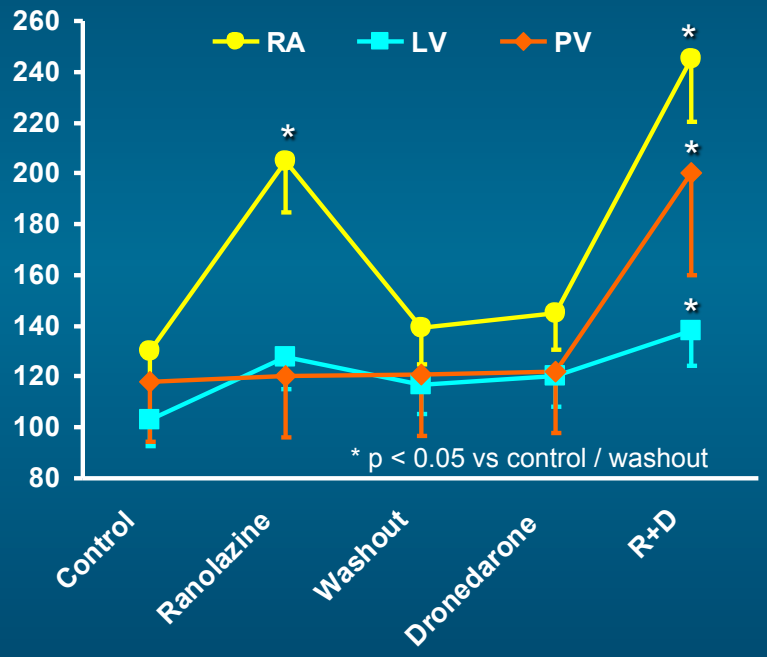


Sossalla S, et al. J Am Coll Cardiol 2010;55:2330–42

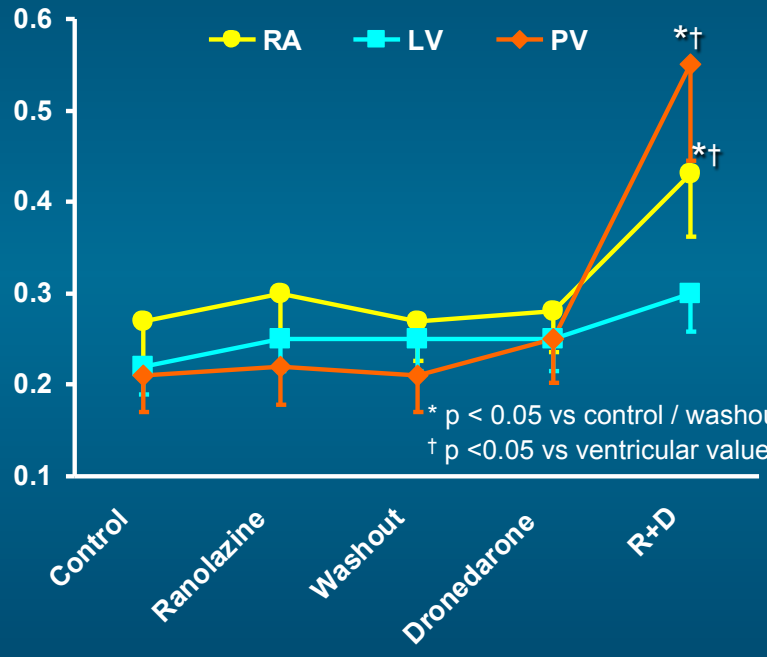
DAD=delayed afterdepolarization; EAD=early afterdepolarization; PV=pulmonary vein

Synergistic Effect on Atrial Excitability of Combination of Ranolazine and Dronedarone

The shortest CL with 1:1 activation, ms

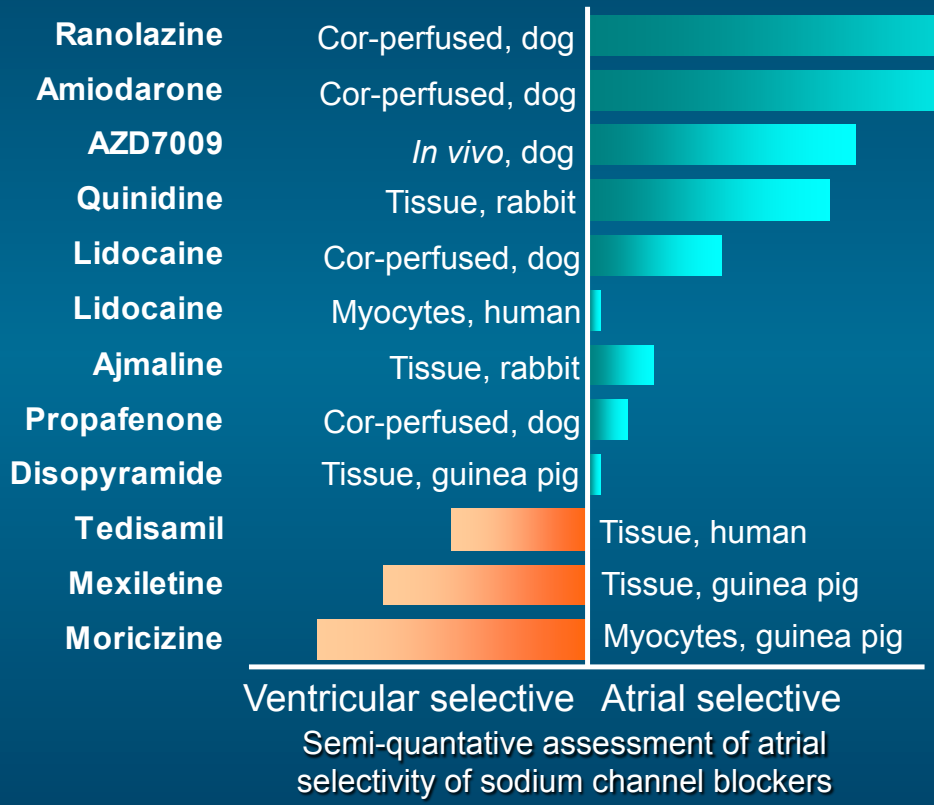


Diastolic threshold of excitation, mA

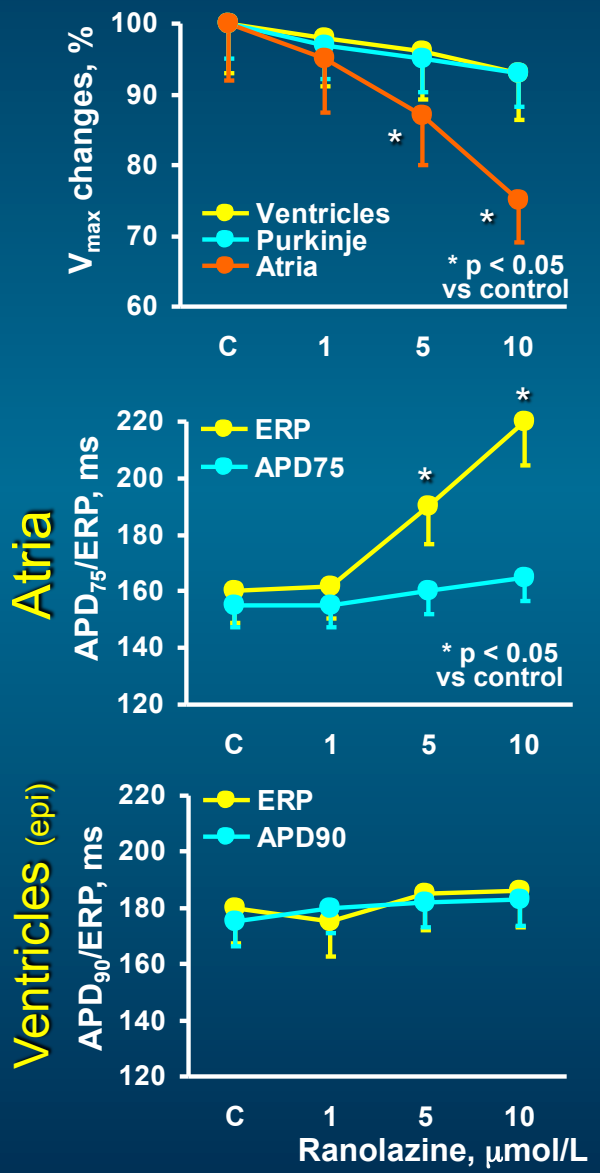


Antzelevitch C, et al. JACC 2010;56:1216-24

Atrial-Selective Sodium Channel Block With Ranolazine



Semi-quantative assessment of atrial selectivity of sodium channel blockers

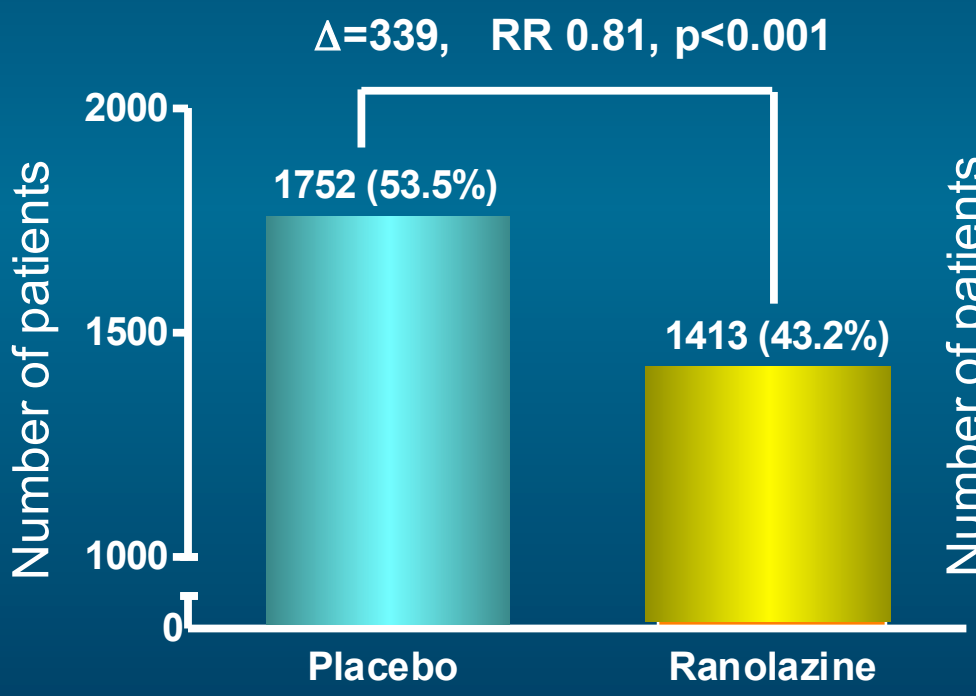


Antzelevitch C, et al. J Cardiovasc Pharm 2008;52:121-8
Burashnikov A, et al. Circulation 2007;116:1449-57

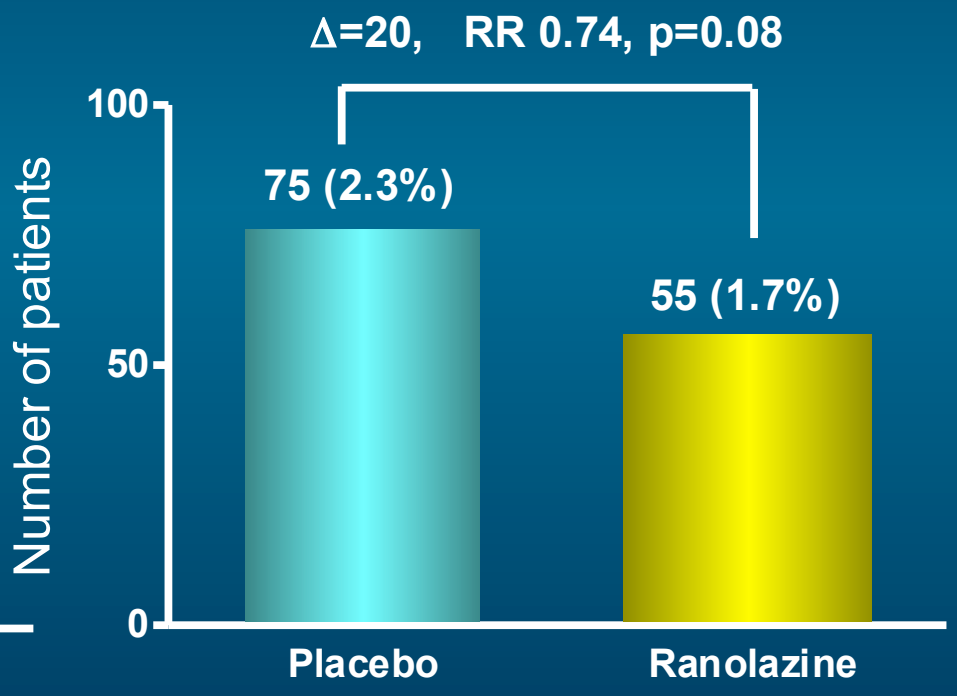
Effect of Ranolazine on SVTs and AF

Merlin-TIMI 36 Trial

Supraventricular tachycardia



New-onset atrial fibrillation

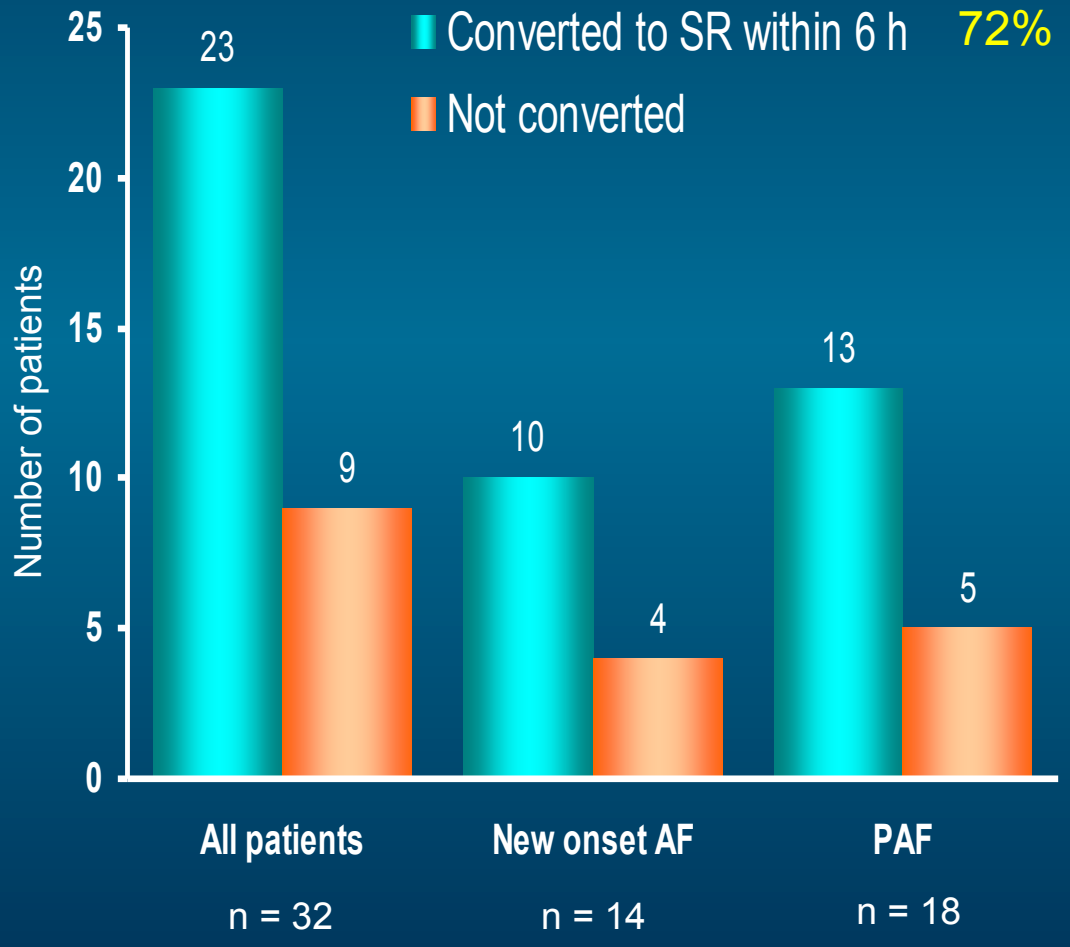


Placebo: n=3,281
Ranolazine: n=3,279

Scirica B, et al. Circulation 2007;116:1647–52

Conversion of Paroxysmal or New Onset AF With Oral Ranolazine: "Pill-in-the-Pocket"

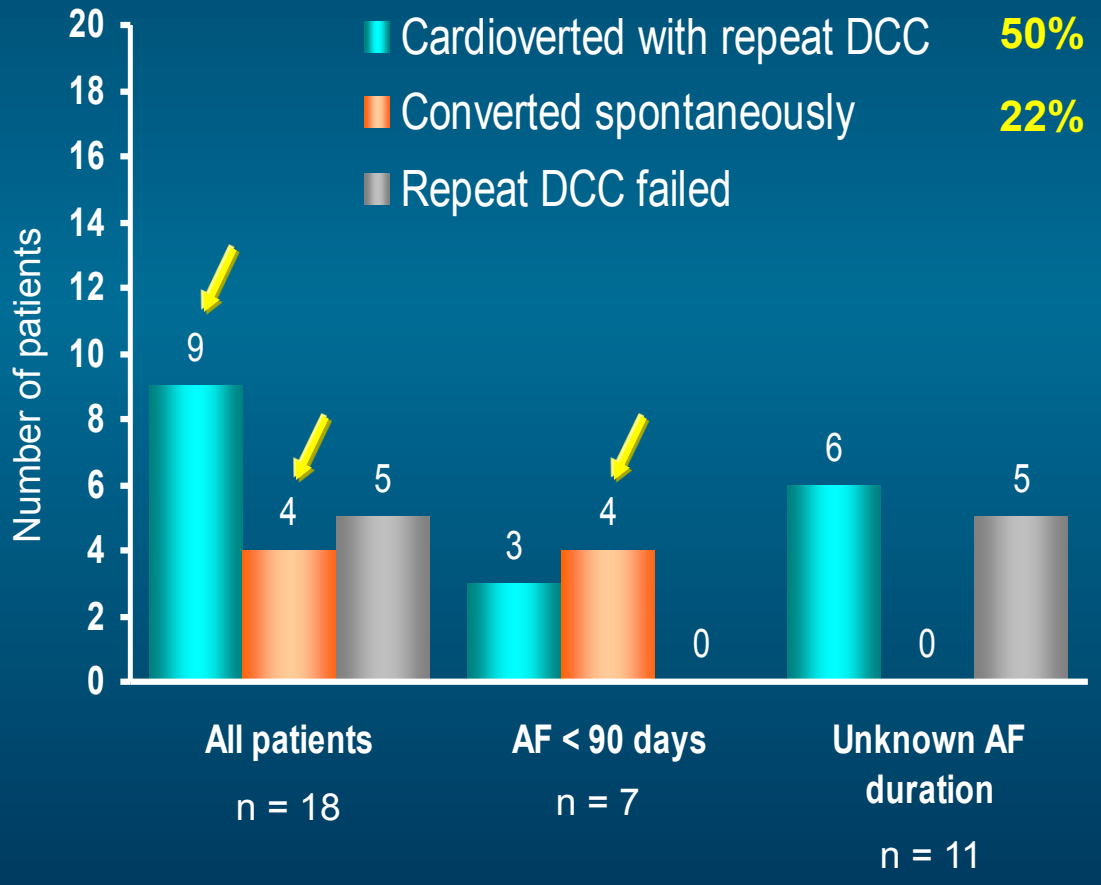
- N = 32 with AF 3-48 h
- 18 (56%) PAF, 14 (44%) new onset AF
- Age 71 ± 9 years, 63% men
- EF 49 ± 12%, ≤ 45% in 11 (33%)
- LAE 69%, CAD 41%, HTN 56%, LVH 25%, CHF 6%
- Ranolazine 2 g p.o.
- 1st dose given in-hospital (69%), office (16%), home (16%)
- Well-tolerated, no hemodynamic or electrophysiologic adverse effects



Murdock D, et al. ACC 2010

Oral Ranolazine Facilitates Cardioversion in Cardioversion Resistant Patients

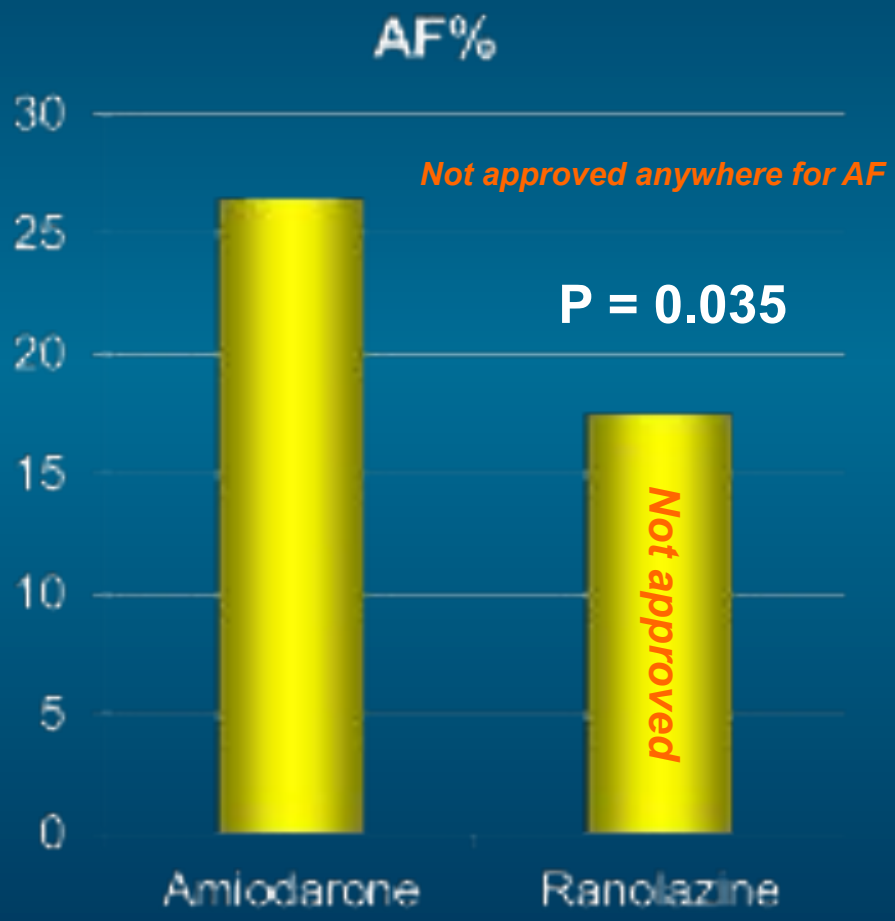
- N = 18 with failed DCC
- Age 65 ± 11 years, 67% men
- EF 62 ± 11%, ≤ 45% in 7 (39%), LAD 44 ± 7 mm
- LAE 67%, CAD 39%, HTN 39%, CHF 22%, DM 22%
- Ranolazine 2 g p.o., no AADs
- DCC repeated 3.5-4 h under the same conditions (pad position, sedation, cardioverter)



Murdock D, et al. ACC 2010

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

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 bdor Placebo
- Treatment duration: 16 weeks or until documented AF recurrence in need of medical intervention
- Recruitment completed (n = 260)

RAFFAELLO: Patient Flow

Screened
n = 310

Screening Failures
n = 69

Randomised
n = 241

n=238
ITT analysis

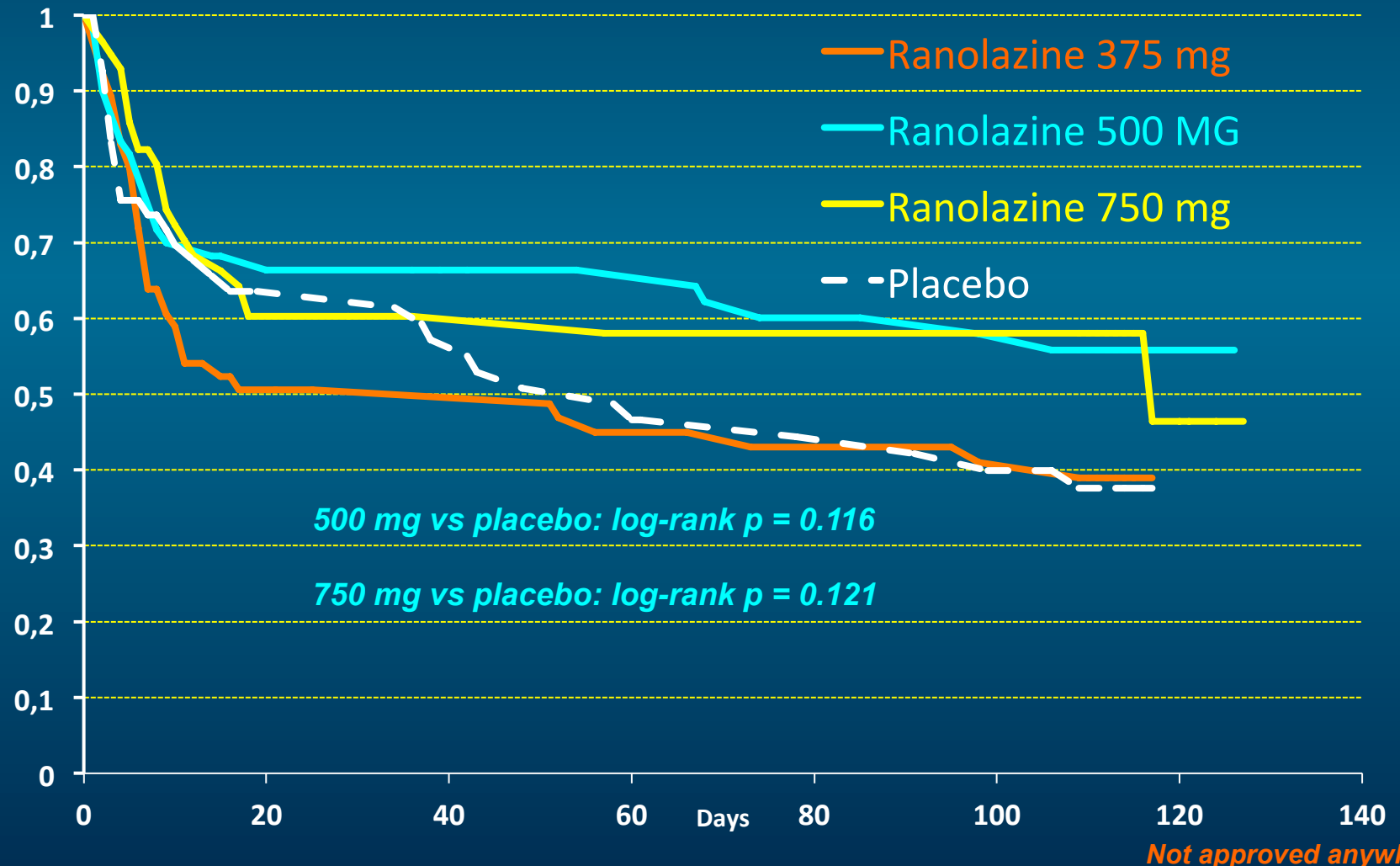
Recurrences
n = 116

Not treated
n = 3

Censored
n = 122

RAFFAELLO Primary Endpoint

Time to 1° AF recurrence (ITT, N=238)



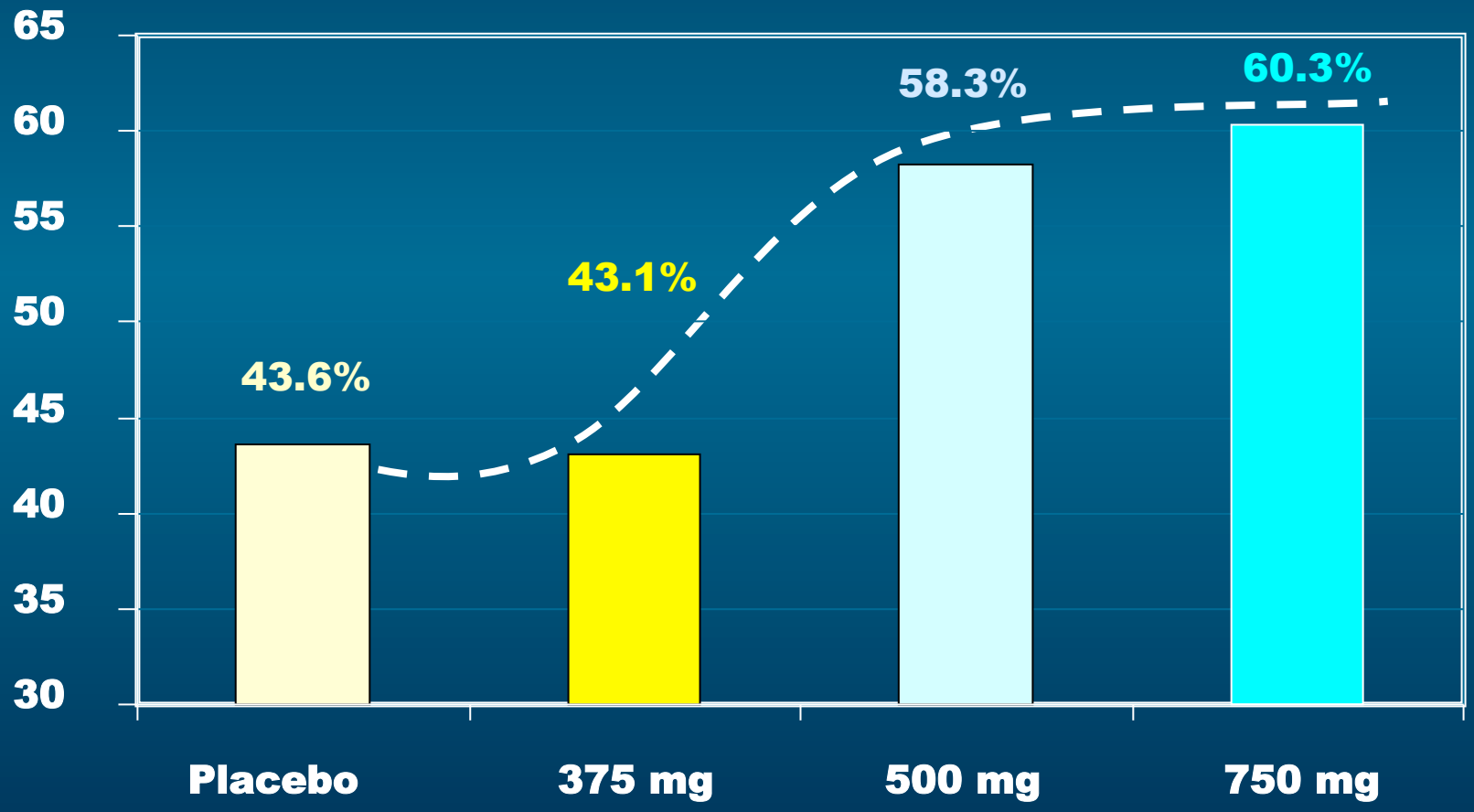
Not approved anywhere

RAFFAELLO - Safety Results

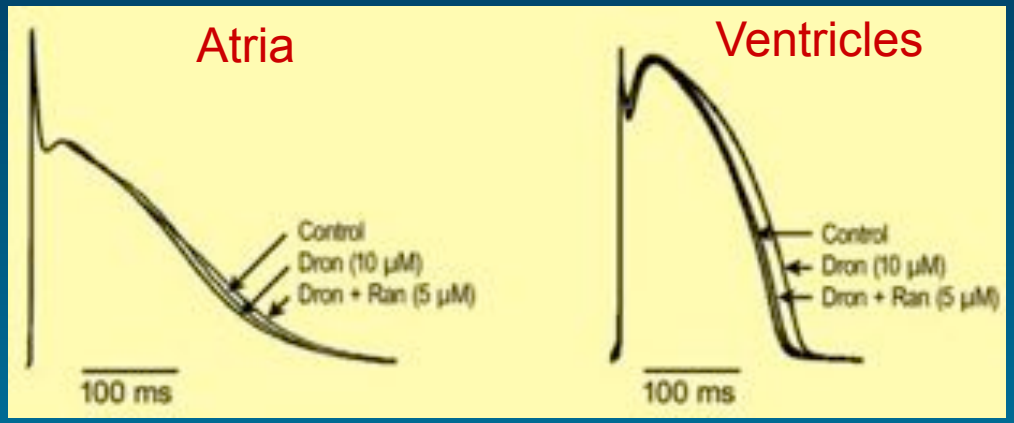
		RAN 375 n=65	RAN 500 n=60	RAN 750 n=58	Placebo n=55	Overall n=238
All Treatment-emergent Signs and Symptoms (n, %pat)						
Overall		51 (78.5%)	46 (76.7%)	42 (72.4%)	41 (74.5%)	180 (75.6%)
Severity	Severe	3 (4.6%)	5 (8.3%)	4 (6.9%)	4 (7.3%)	16 (6.7%)
SAE	Yes	2 (3.1%)	3 (5.0%)	3 (5.2%)	4 (7.3%)	12 (5.0%)
Related Treatment-emergent Signs and Symptoms (n, %pat)						
Overall		12 (18.5%)	10 (16.7%)	20 (34.5%)	8 (14.5%)	50 (21.0%)
Severity	Severe	1 (1.5%)	1 (1.7%)	1 (1.7%)	1 (1.8%)	4 (1.7%)
SAE	Yes	1 (1.5%)	0	2 (3.4%)	1 (1.8%)	4 (1.7%)

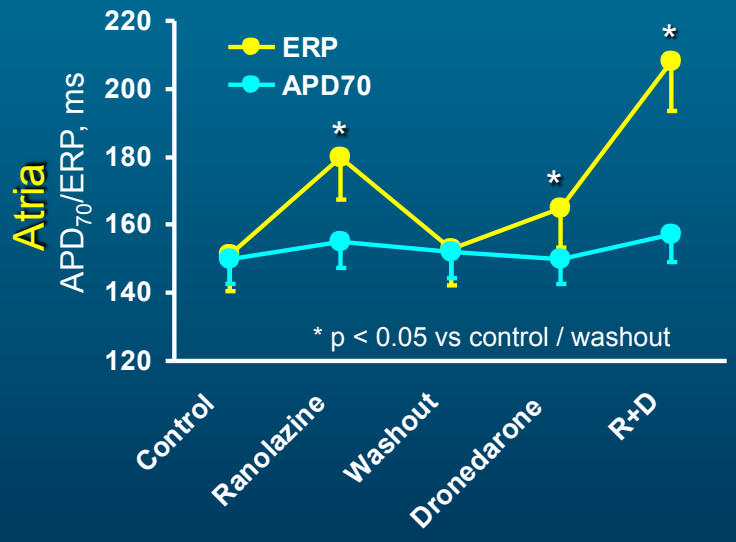
The most common treatment-related TESS (≥ 5% in any treatment group) were constipation, nausea, dizziness, asthenia, and fatigue. The incidence was highest in the Ranolazine 750 mg group (5.2-8.6%, respectively).

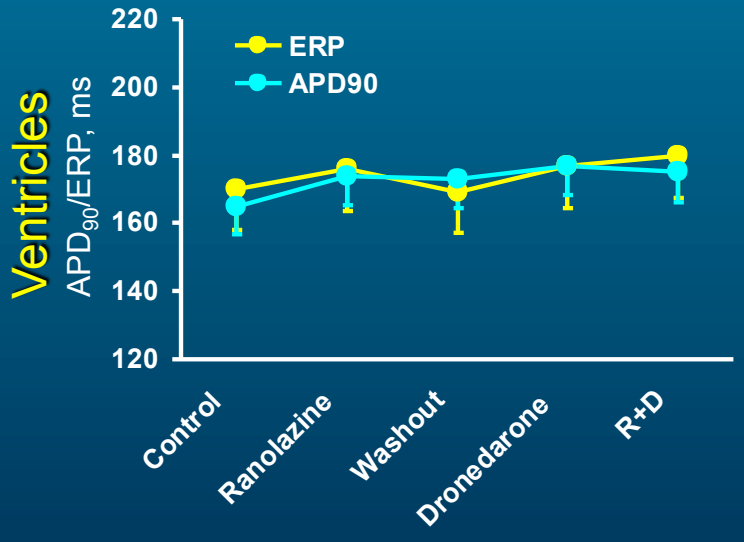
Exploratory Analysis
Freedom from AF at Different Doses



Synergistic Effect on Atrial PRR of Combination of Ranolazine and Dronedarone



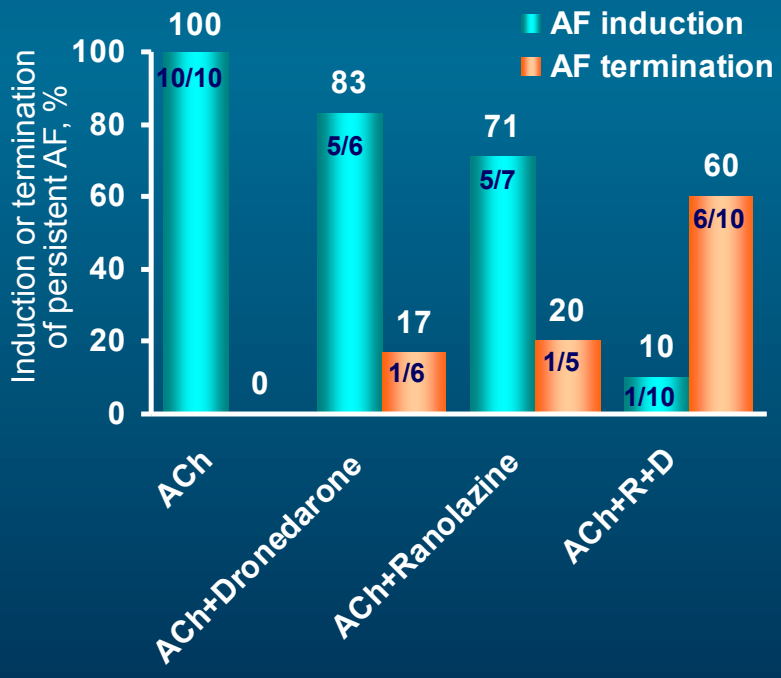




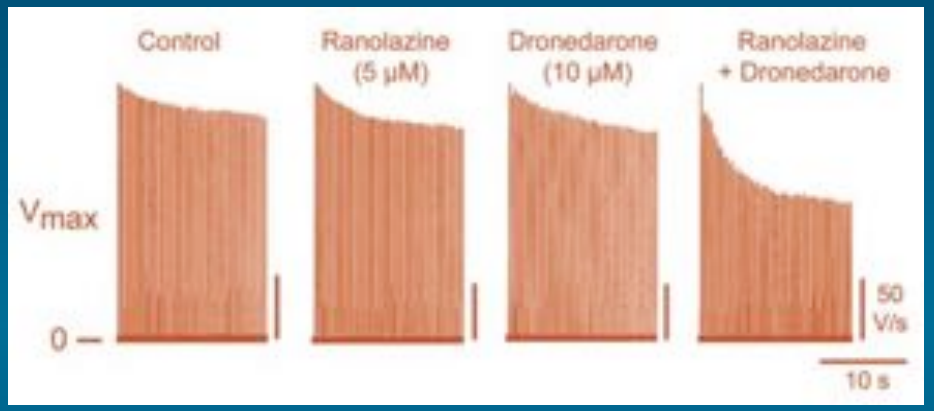
Antzelevitch C, et al. JACC 2010;56:1216-24

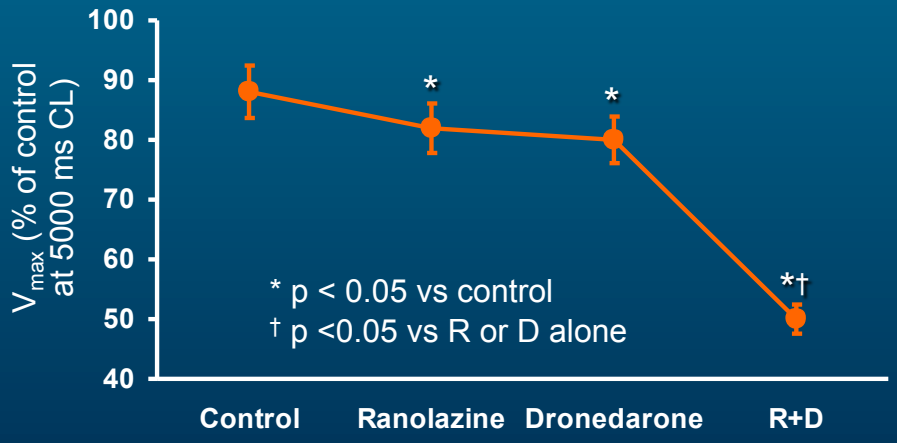
Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

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



Pulmonary vein preparations

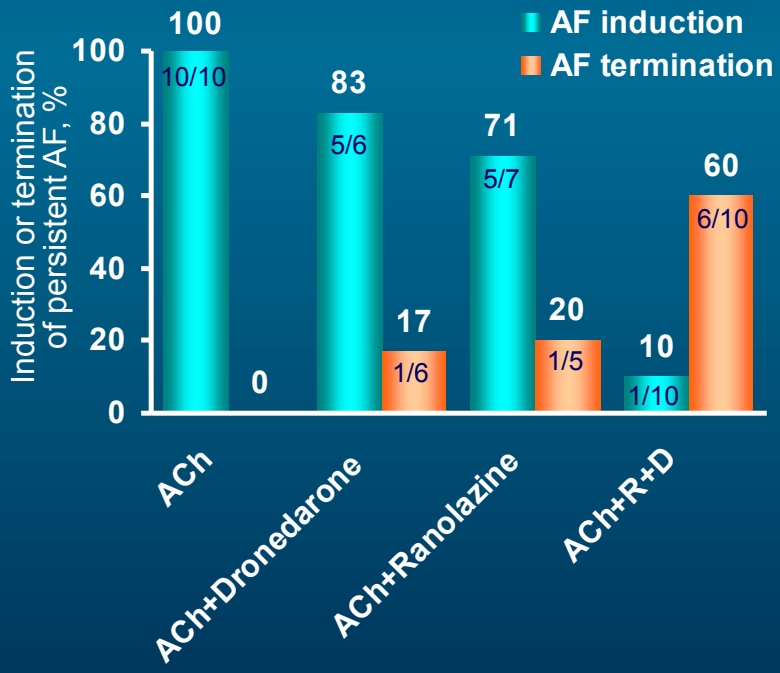




Burashnikov A, et al. J Am Coll Cardiol 2010;56:1216–24

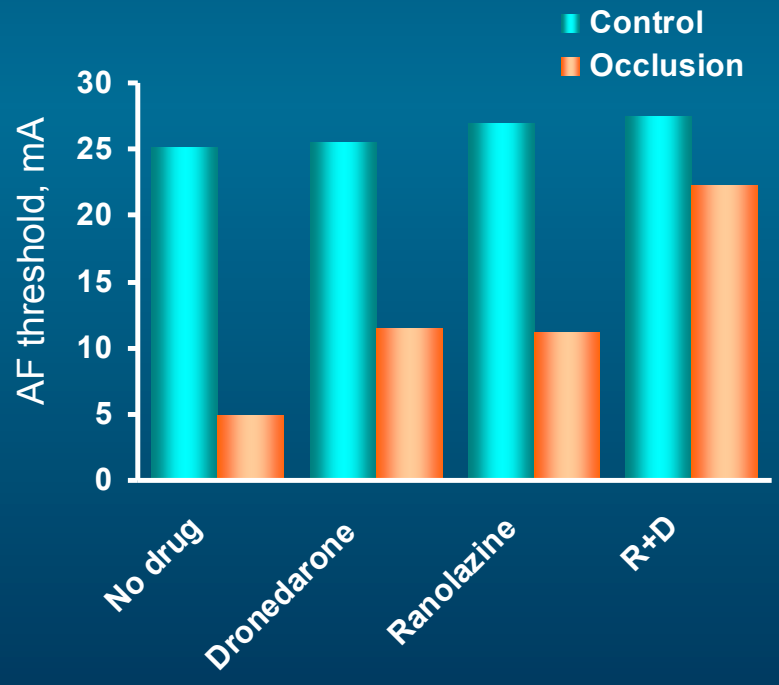
Synergistic Effect of Combination of Ranolazine and Dronedarone

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



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

- Open-chest Yorkshire pigs
- Proximal LCX occlusion (75%)
- Ranolazine i.v. 0.6 mg/kg+0.035 mg/kg/min
- Dronedarone i.v. 0.5 mg/kg

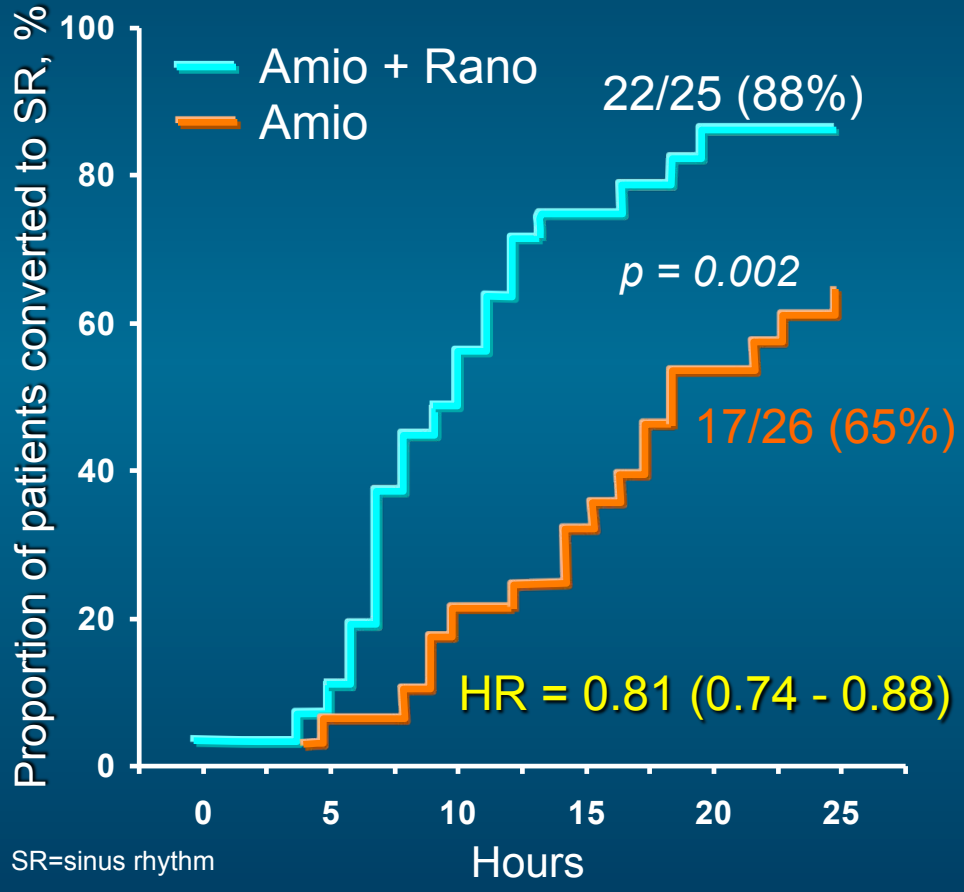


Verrier RL, et al. Heart Rhythm 2012 [In press]

Not approved anywhere

Pharmacological Cardioversion of AF
Combination of Amiodarone and Ranolazine

- 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)

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

Not approved anywhere

A Phase 2, Proof of Concept, Randomized, Placebo-Controlled, Parallel Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination on Atrial Fibrillation Burden in Subjects with Paroxysmal Atrial Fibrillation

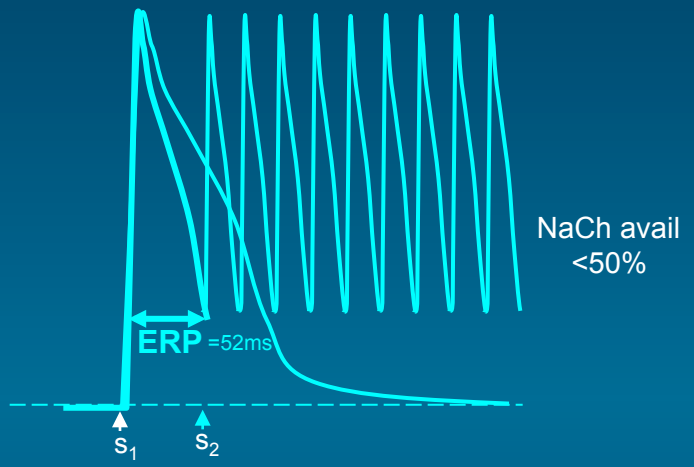
HARMONY
A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

Combination Therapy: I_{Kr} + I_{Na} Inhibition

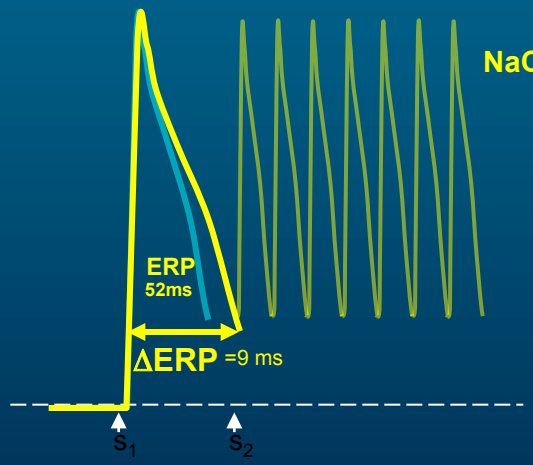
↑ Atrial ERP
- ↑ APD - ↓I_{Kr}
- ↑ PRR - ↓Peak I_{Na} (ERP - APD)

PRR - slow recovery of membrane excitability after a preceding action potential

S2-induced AF (no drug)

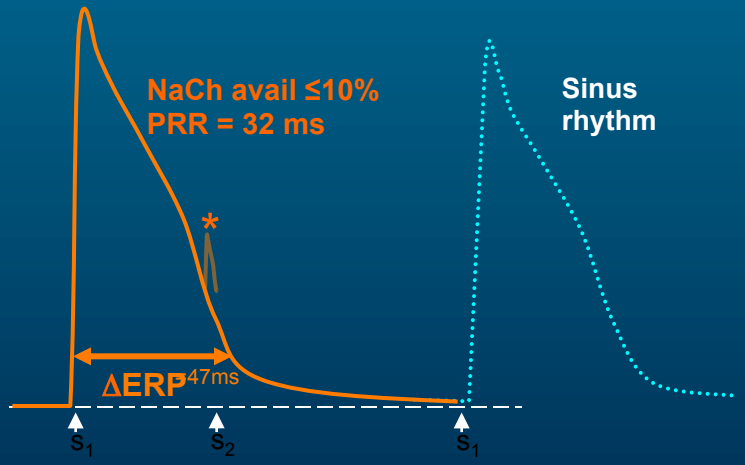


AF + I_{Kr} channel block



I_{Na} block alone:
ΔERP=20 ms

AF + I_{Kr} + I_{Na} channel block



Rajamani and Belardinelli, Gilead on file, 12/2011

HARMONY
A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

Background

- **Ranolazine (Ran): antianginal approved in 2005**
- **Dronedarone (Dron): anti-AF approved in 2009**
- **Ran and Dron are multi-ion channel blockers**
  - **Ran**: ↓ peak and late I_{Na} (↓ I_{Kr} moderate)
  - **Dron**: ↓ I_{Kr}, ↓ I_{KACh}, ↓ I_f (↓ peak I_{Na})

} In atrial myocytes*

- **Mechanism for synergism**
  - **inhibitions of peak INa (Ran >> Dron) and IKr (Dron >> Ran)**
- **Mechanism for safety**
  - concentrations of Dron 1.6 - 3 fold below the IC_{50} to inhibit I_{CaL}
  - Inhibition of late I_{Na} stabilizes ventricular repolarization

*At plasma concentrations achieved by Ran=750 mg bid; Dron=150 or 225 mg bid (HARMONY doses)

Burashnikov, Belardinelli, Antzelevitch et al. JACC 56: 1216-1224, 2010 Wu, Li, Belardinelli. Gilead on file, 04/2011 Jia, Hoyer, Belardinelli. Gilead on file, 07/2011 Verrier, Belardinelli *et al. Heart Rhythm* **10**: 121-127, 2013

Ranolazine/Dronedarone Synergy

- **Mechanism for synergism**
  - **Ranolazine and Dronedarone are multi-ion channel blockers**
    - Inhibitions of peak I_{Na} (Ran >> Dron) & I_{Kr} (Dron >> Ran)
    - Inhibition of late I_{Na} stabilizes ventricular repolarization and suppresses triggered activity
- **Safety**
  - Cardio-depressant effects of Dronedarone are concentration-dependent
  - Plasma concentrations achieved by Dronedarone 225 mg in combination with Ranolazine 750 mg (HARMONY dose) were ≥50% lower than MULTAQ (*Phase 1 DDI study*) and were not cardio-depressant (*in vitro* studies)
  - Inhibition of late I_{Na} prevents VT

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A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

Objective

To determine if a combination therapy comprised of a moderate dose of ranolazine and low dose dronedarone is superior to each drug alone, and to placebo, in reducing AF burden in patients with implanted pacemakers who have paroxysmal AF and are off of any antiarrhythmic drug

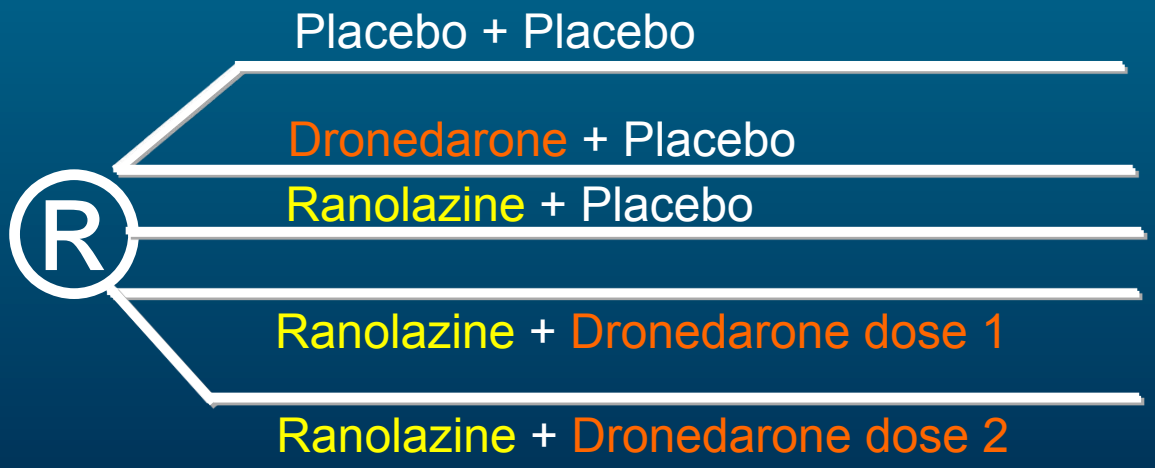
Note: AF burden = total time a subject was in AF expressed as a percentage of total recording time

HARMONY

A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal AF

- PAF with pacemakers
- N = 150, 45 centres
- Follow-up: 12 weeks
- **Ranolazine vs Dronedarone vs Ranolazine + Dronedarone**
- Primary endpoint: reduction in AF burden
- 2^0 endpoints: AF burden at each visit (4, 8, 12 weeks) and # episodes



Available at: http://clinicaltrials.gov/show/NCT01522651

HARMONY
A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

Enrollment and Study Oversight

355 patients screened, 134 randomized

Germany	Italy	Israel	Netherlands	Poland	UK	US
						
24		25		60		23

Randomized ≥ 5 patients

J. Wilczek; Katowice, PL (10)
M. Swissa; Rehovot, IS (8)
K. Wranicz; Lodź, PL (8)
D. Czarnecka; Kraków, PL (7)
S. Kääb; Műnchen, GE (7)
G. Raczak; Gdańsk,PL (7)
L. Maier; Göttingen, GE (6)
N. Freedberg; Afula, IS (5)
M. Grabowski; Warszawa,PL (5)

Randomized ≥ 3<5 patients

A. Katz; Ashkelon, IS (4)
E. Nowalany-Kozielska; Zabrze, PL (4)
B. Winkelmann; Frankfurt, GE (4)
A. Cohen; Auora, USA (3)
G. Jaworska; Toruń, PL (3)
D. Murdock; Wausau, USA (3)
W. Musial; Bialystok, PL (3)
A. Przybylski; Warszawa, PL (3)
J. Schrickel; Bonn, GE (3)

Scientific Committee

J.Camm, Univ of London, UK
P.Kowey, Main Line Health, PA, USA
J.Reiffel, Columbia UMC, NY, USA

EP Core Lab and Adjudication Committee:

W. Zareba, S. Rosero, M.Brown
University of Rochester, Rochester, NY

Independent Medical Reviewer:

A. Waldo
Case Western Reserve University
Cleveland, OH

HARMONY
A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

Entry Criteria

Inclusion Criteria:

- Paroxysmal AF
- Dual chamber pacemaker
  - Implanted at least 3 months prior to screening
  - Atrial arrhythmia algorithm detection
- AF Burden ≥ 2% and ≤ 70% at randomization

Major Exclusion Criteria:

- Persistent / Permanent AF
- History of AFl/AT without successful ablation
- NYHA Class III & IV or Class II with recent decompensation
- Recent history of LVEF<40%
- Stroke, MI, unstable angina, or CABG 3 months prior screening
- LFTs>2xULN, CrCL ≤ 30 mL/min
- CYP3A strong inhibitors or inducers
- AAD Class I/III (within 5-half lives), amiodarone (3 months)
- Use of dabigatran, digitalis, metformin (>1000 mg daily)

HARMONY
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Endpoints

- **Primary endpoint:**
  - **Change from baseline in AF burden over 12 weeks**
- Key secondary endpoints:
  - Change in AF burden at each study visit
  - Percentage of patients with 50% burden reduction
  - Change in number and duration of AF episodes
  - Change in AF rate
- Safety and tolerability of each component and the combination

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Baseline Characteristics & CV History

	Placebo N=26	Ran750 N=26	Dron225 N=26	RD150 N=26	RD225 N=27
	n (%)				
Age (yrs) Mean (SD)	72 (8.4)	70 (10.8)	75 (7.8)	73 (9.4)	71 (7.1)
Male n (%)	13 (50)	10 (39)	10 (39)	15 (58)	15 (56)
Hypertension	20 (77%)	24 (92%)	22 (85%)	22 (85%)	22 (82%)
Heart failure	7 (27%)	6 (23%)	3 (11%)	3 (11%)	5 (18%)
LV Ejection Fraction % mean (SD)	56 (6)	57 (10)	59 (8)	57 (8)	57 (8)
CAD	8 (31%)	7 (27%)	10 (39%)	9 (35%)	8 (30%)
Prior Cardioversion	3 (11%)	11 (42%)	10 (38%)	7 (27%)	5 (18%)
Ablation Atrial Fibrillation AV node	3 (11%) 3 (11%) 0	6 (23%) 2 (8%) 4 (15%)	3 (11%) 3 (11%) 0	2 (8%) 1 (4%) 1 (4%)	7 (26%) 4 (15%) 3 (11%)
Prior AAD Use (Chronic)	9 (41%)	12 (50%)	16 (64%)	5 (21%)	13 (52%)

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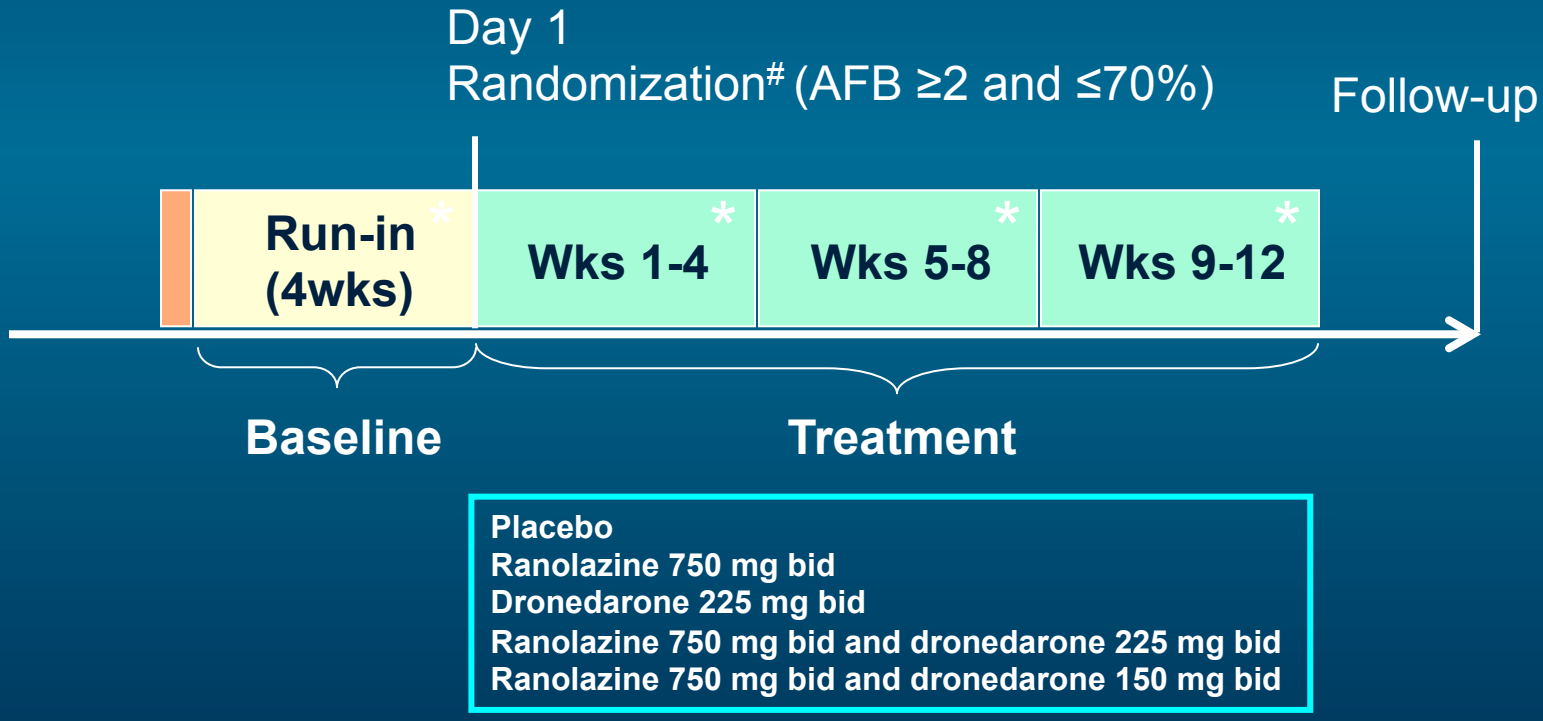
Study Objective and Overview

- To determine if combination therapy with moderate dose ranolazine and low dose dronedarone is superior to each of the components and to placebo in reducing AF burden in patients with implanted pacemakers who have paroxysmal AF



Stratified by AFB<15% and >15%

* PPM Interrogation → Results to Core EP lab (EGMs adjudicated)

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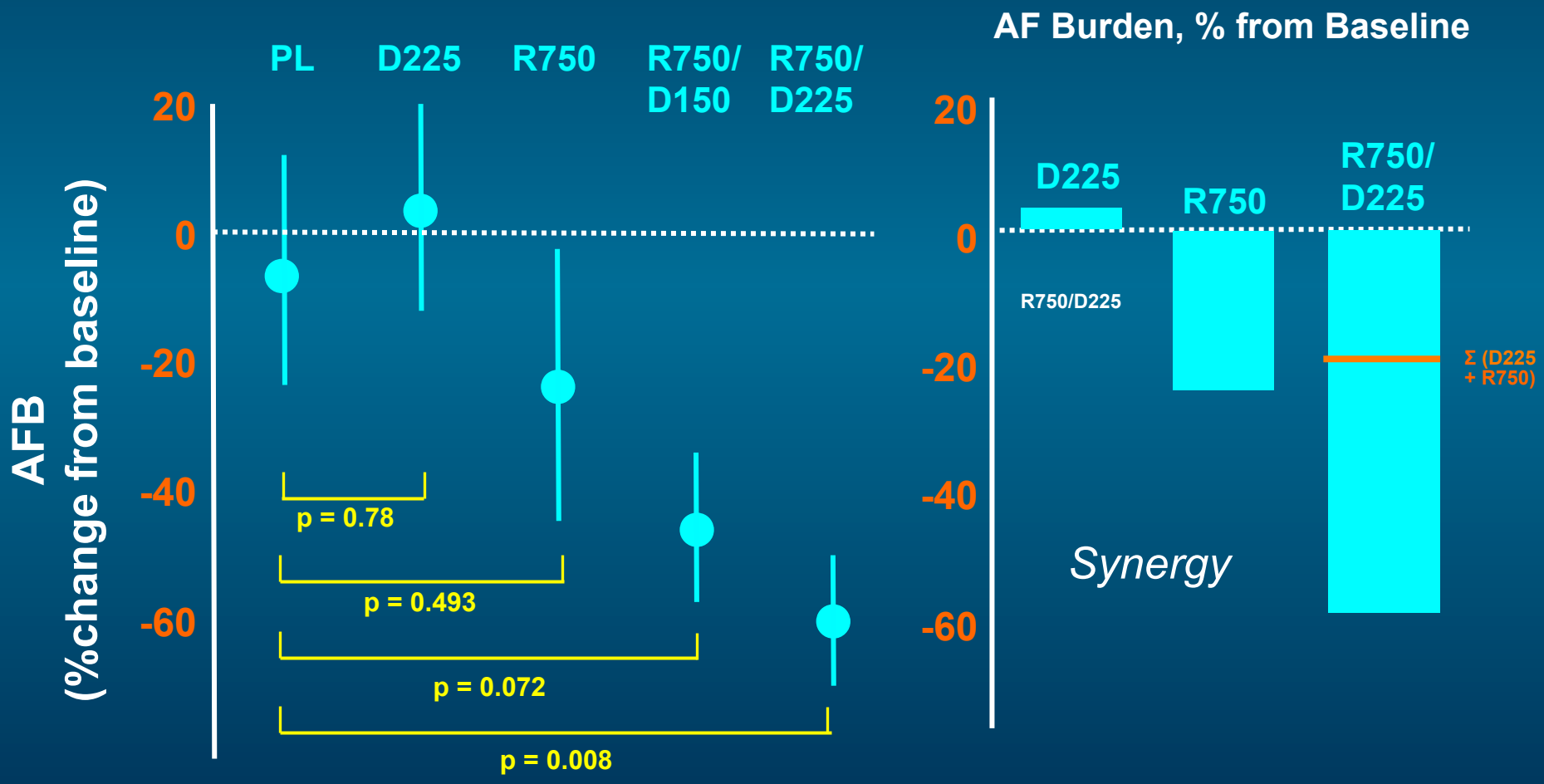
Primary Endpoint: % Change from Baseline in AFB over 12 weeks



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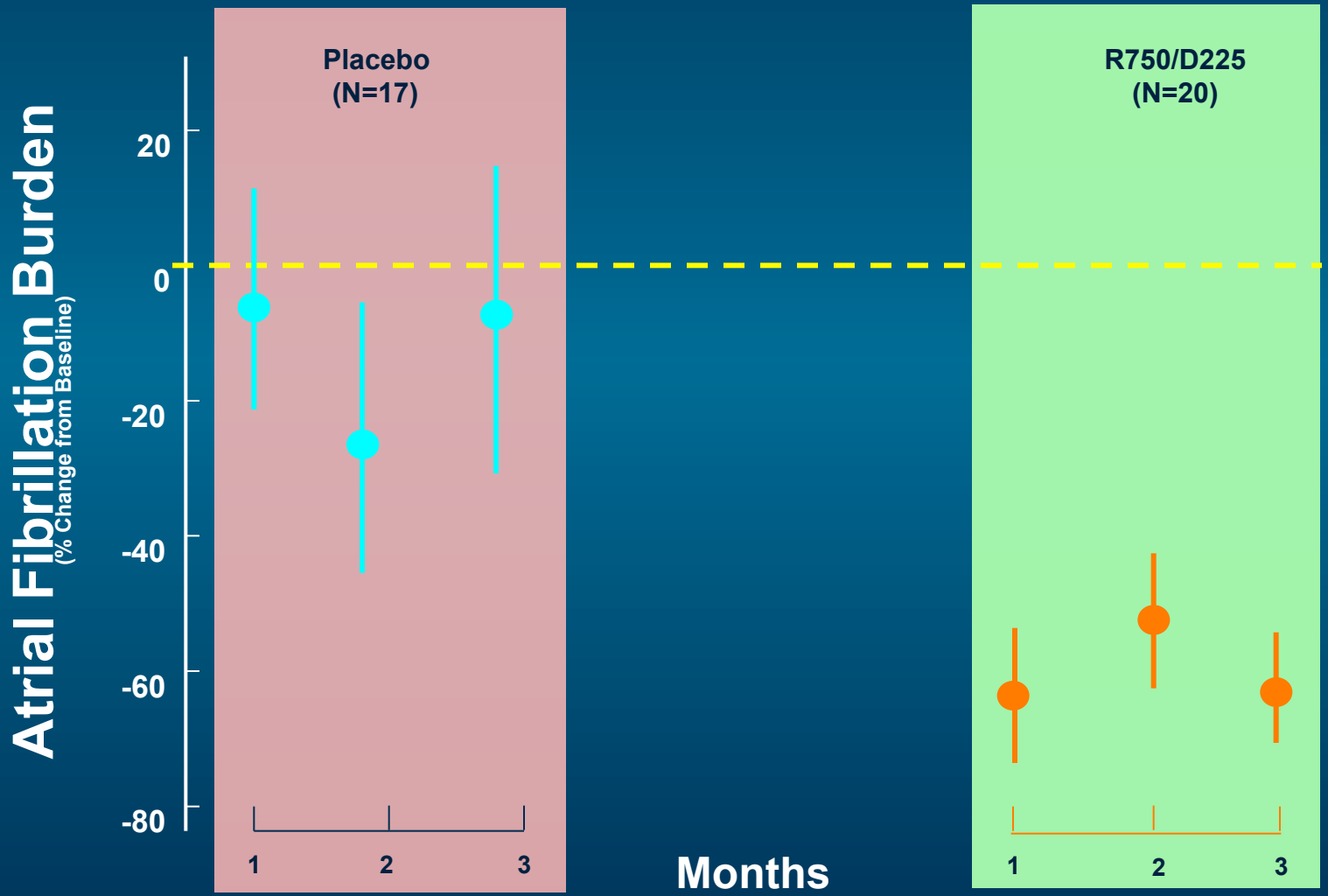
Change in AF Burden by Month



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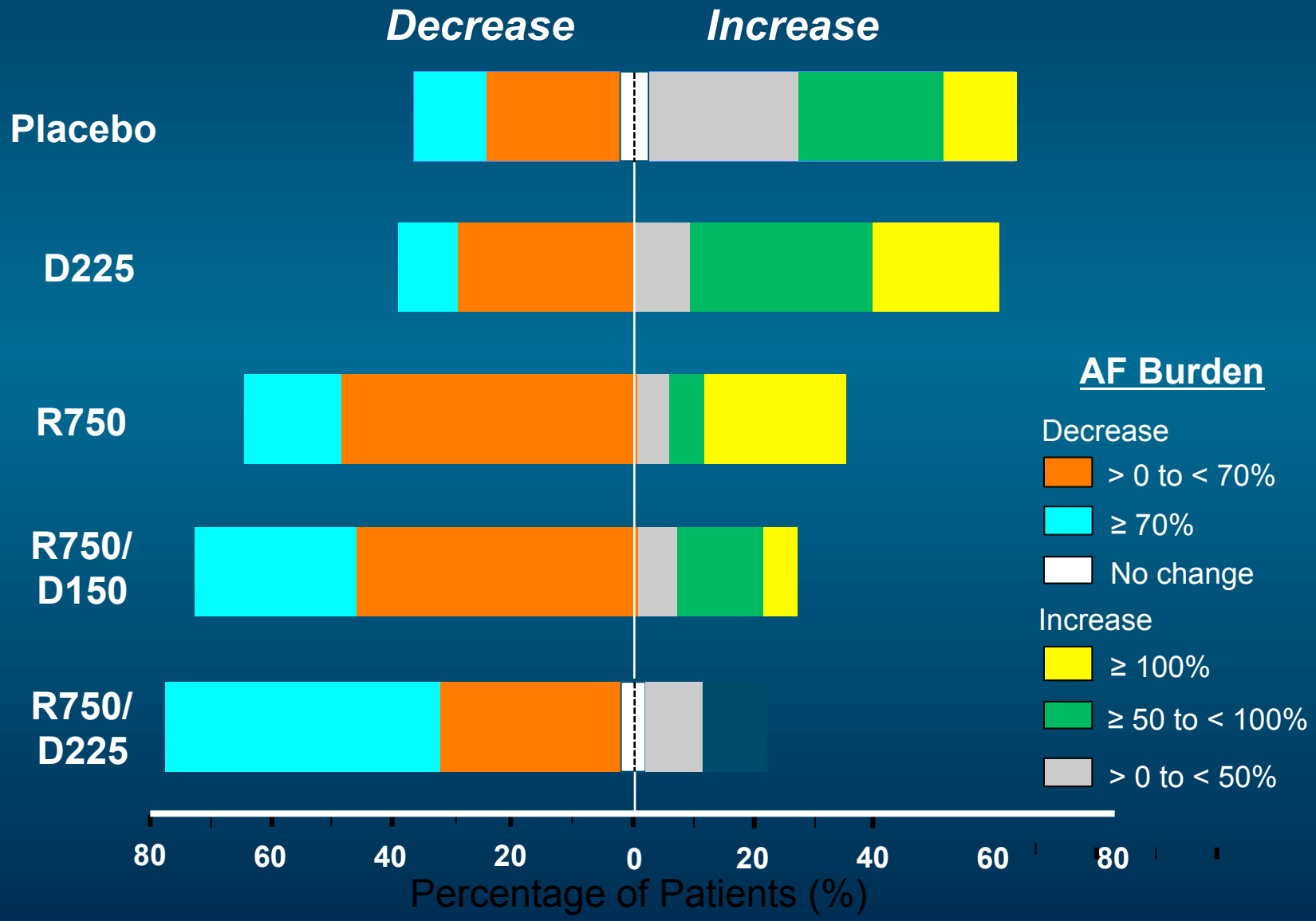
Changes from Baseline in AFB Over 12 Weeks



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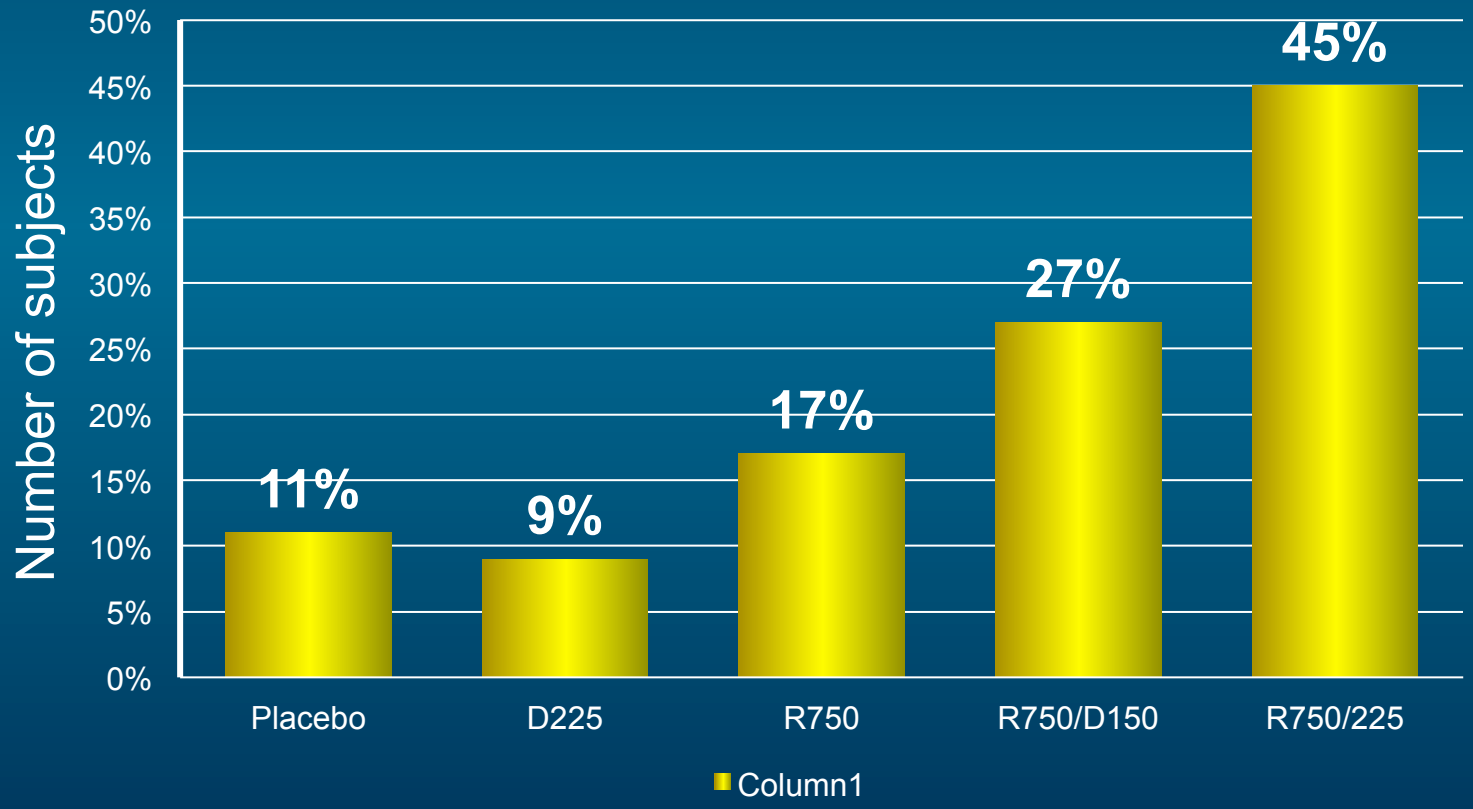
Subjects with ≥70% Reduction in AF burden Over 12 Weeks



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Overview of Safety

Subjects with any Treatment Emergent:	Placebo N=26	Ran750 N=26	Dron225 N=26	RD150 N=26	RD225 N=27
			n (%)		
Adverse event (AE)	15 (58%)	17 (65%)	18 (69%)	16 (61%)	20 (74%)
Serious adverse event (SAE)	1 (4%)	7 (27%)	2 (8%)	1 (4%)	5 (18%)
AE leading to premature study drug discontinuation	3 (11%)	5 (19%)	4 (15%)	5 (19%)	5 (18%)

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Overview of Safety

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Most Frequent AEs

	Placebo N=26	Ran750 N=26	Dron225 N=26	RD150 N=26	RD225 N=27
	n				
Atrial fibrillation	2	3	4	3	1
Dizziness	1	3	2	2	0
Constipation	0	1	1	4	1
INR increased	0	2	1	2	2
Nausea	0	3	1	1	2
Diarrhea	0	2	2	1	1
Dyspnea	1	1	2	1	1
Fatigue	0	3	0	1	2
Hypotension	0	0	0	1	3

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QT_{CB} Changes from Baseline at Week 12

	Placebo	D225	R750	R750/D150	R750/D225
Baseline	428 ± 52 (18)	422 ± 32 (17)	426 ± 37 (16)	430 ± 24 (10)	432 ± 28 (16)
Week 12	432 ± 38 (7)	430 ± 29 (10)	429 ± 34 (8)	432 ± 29 (10)	425 ± 25 (9)
Δ QT_c	3	7	-6	-13	1

Values are mean ± SE in msec

( ) = number of patients

includes only patients with pair QT_c values (baseline and week 12)

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	Placebo	D225	R750	R750/D150	R750/D225
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Δ QT_c	3	7	-6	-13	1

Values are mean ± SE in msec

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Summary/Conclusions

- Greater efficacy of the combination RD225 to reduce AF burden when compared to placebo and to either Ran750 or Dron225 alone
- Acceptable safety/tolerability profile: the incidences of AEs, SAEs or AEs leading to discontinuation were similar in the combination RD225 group compared to the sum of R750 + D225

Thank you for your attention

St George's
University of London

Adherence and Persistence to Therapy

“Drugs don’t work in patients who don’t take them.”

I have been working on a paper exploring the link between physician-patient communication and medication adherence and the implications for health care costs. Medication nonadherence among patients is and has been a “gigantic” problem for the health care industry over the last 20 to 30 years… and not just for pharma. Patients outcomes suffer and health care cost sky rocket as nonadherent patients fill ER and hospitals across the U.S.

C. Everett Koop, former Surgeon General of the US