DRONEDARONE

A New Anti-Arrhythmic Drug
for the Treatment of Atrial Fibrillation/Atrial Flutter

Dronedarone is approved by the FDA and under EMEA review. All information is provided for scientific purpose exclusively. Multaq no se encuentra comercializado en España.

GLM.DRO.09.07.14

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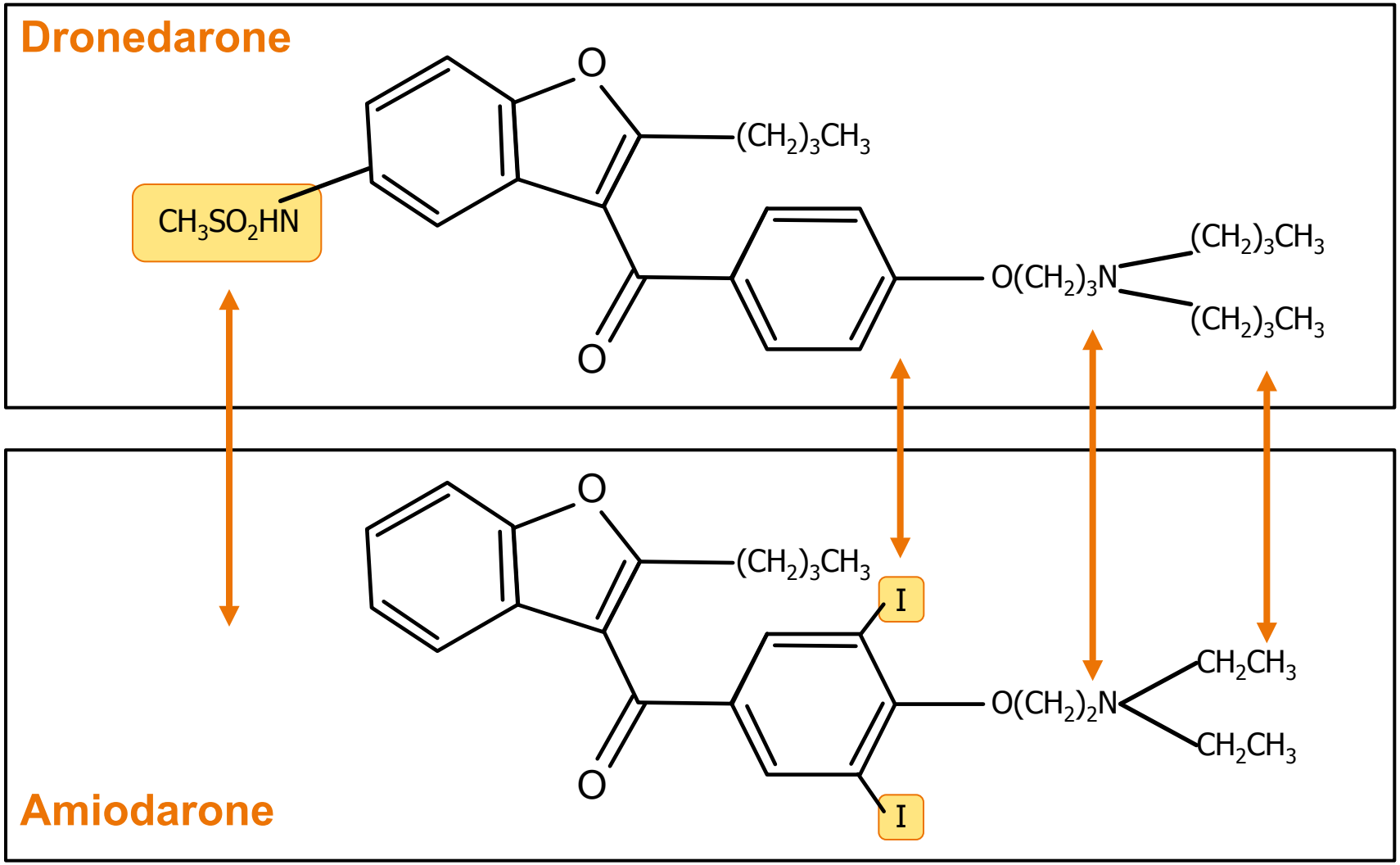
Section 1 Dronedarone background

1b Key safety trials

1a Pharmacology and Mechanism of Action

Dronedarone has Key Structural Differences to Amiodarone



Kathofer *et al. Cardiovasc Drug Rev.* 2005;23(3):217-30.

Pharmacological Profile of Dronedarone

- Absorption
  - 70%-94% absorption in healthy subjects
  - First-pass effect results in absolute bioavailability of ~15%
  - Tmax = 3-5 hours
  - Food increases bioavailability by 2- to 4.5-fold
- Distribution
  - Highly bound (>99%) to human plasma protein (mostly albumin)
  - Mean volume of distribution of 1,440 to 3,440 L (after IV administration)
- Metabolism
  - Extensively metabolized, mainly by CYP3A4
  - Metabolite SR35021 may contribute to the pharmacologic activity of dronedarone (3-10x less potent)
- Excretion and Elimination
  - Major route of excretion is in feces (84%)
  - No unchanged dronedarone is excreted in urine
  - Terminal half-life of dronedarone is 20-40 hours after repeated administration of 400mg BID
  - Steady state reached within 4-8 days

Data on file.

Dronedarone is a Multichannel Blocker

- Dronedarone Possesses Electrophysiologic Characteristics of all Four Vaughan Williams Classes
  - Outward currents
    - Ikr: rapidly activating delayed rectifier potassium current (ventricle)
    - Iks: slowly activating delayed rectifier potassium current (ventricle)
    - Ito: transient outward current
    - Ik(Ach): muscarinic receptor-operated K+ current (atrium)
  - Inward currents
    - Fast sodium currents
    - Calcium channel antagonist

Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-426.

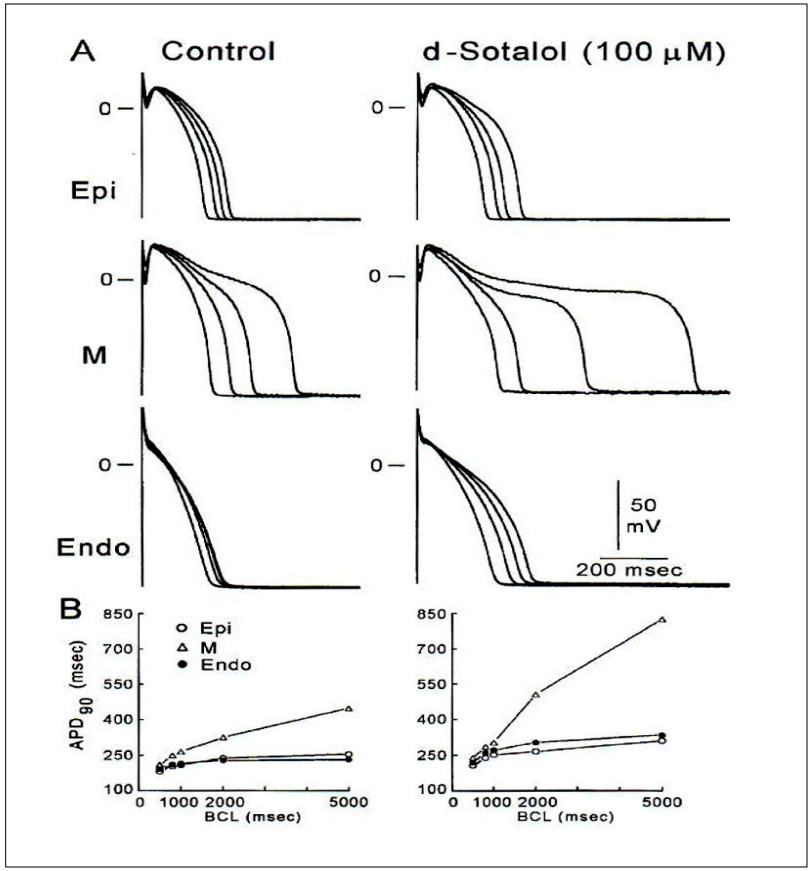
Dronedarone possesses a very low proarrhythmic profile

- Dronedarone induces a homogenous effect on ventricular repolarisation
- Dronedarone effect on action potential duration shows no reverse-use dependency
- Dronedarone suppresses early after-depolarisation induced by pure class III agents

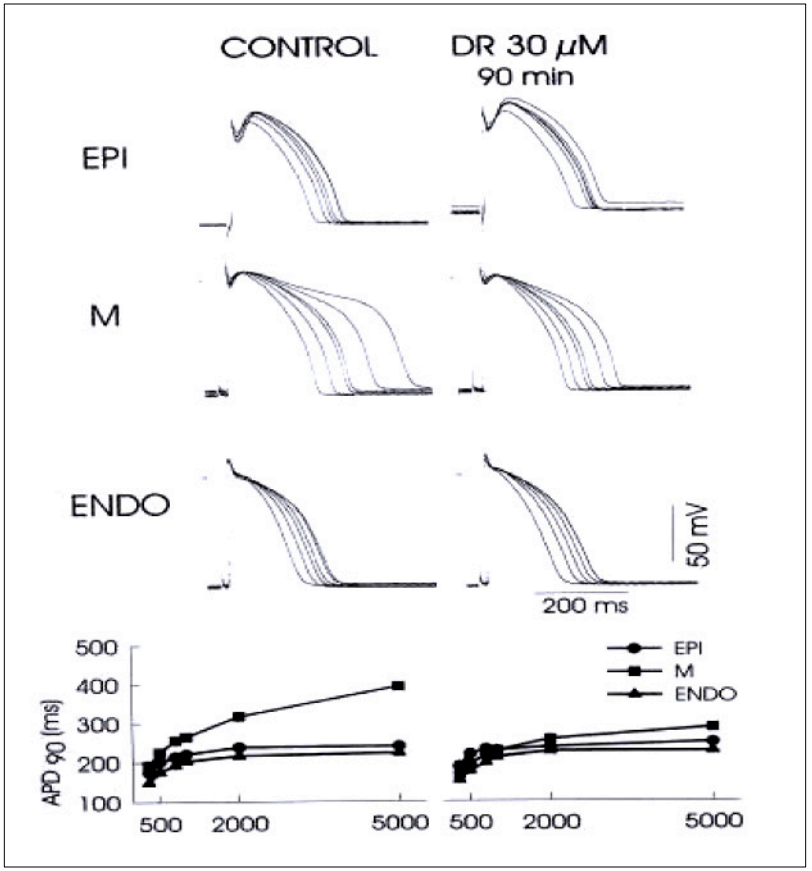
Sicouri S, *Fund Clin Pharmacol*. 1999;13:72.
Sun W, *et al. J Cardiovasc Pharmacol*. May 2002;39(5):677-684.
Varro A, *et al. Brit J Pharmacol*. 2001;133:625-634.

Dronedarone Reduces Transmural Dispersion of Ventricular Repolarization

Effects of d-sotalol and dronedarone on transmural repolarization of the dog ventricle

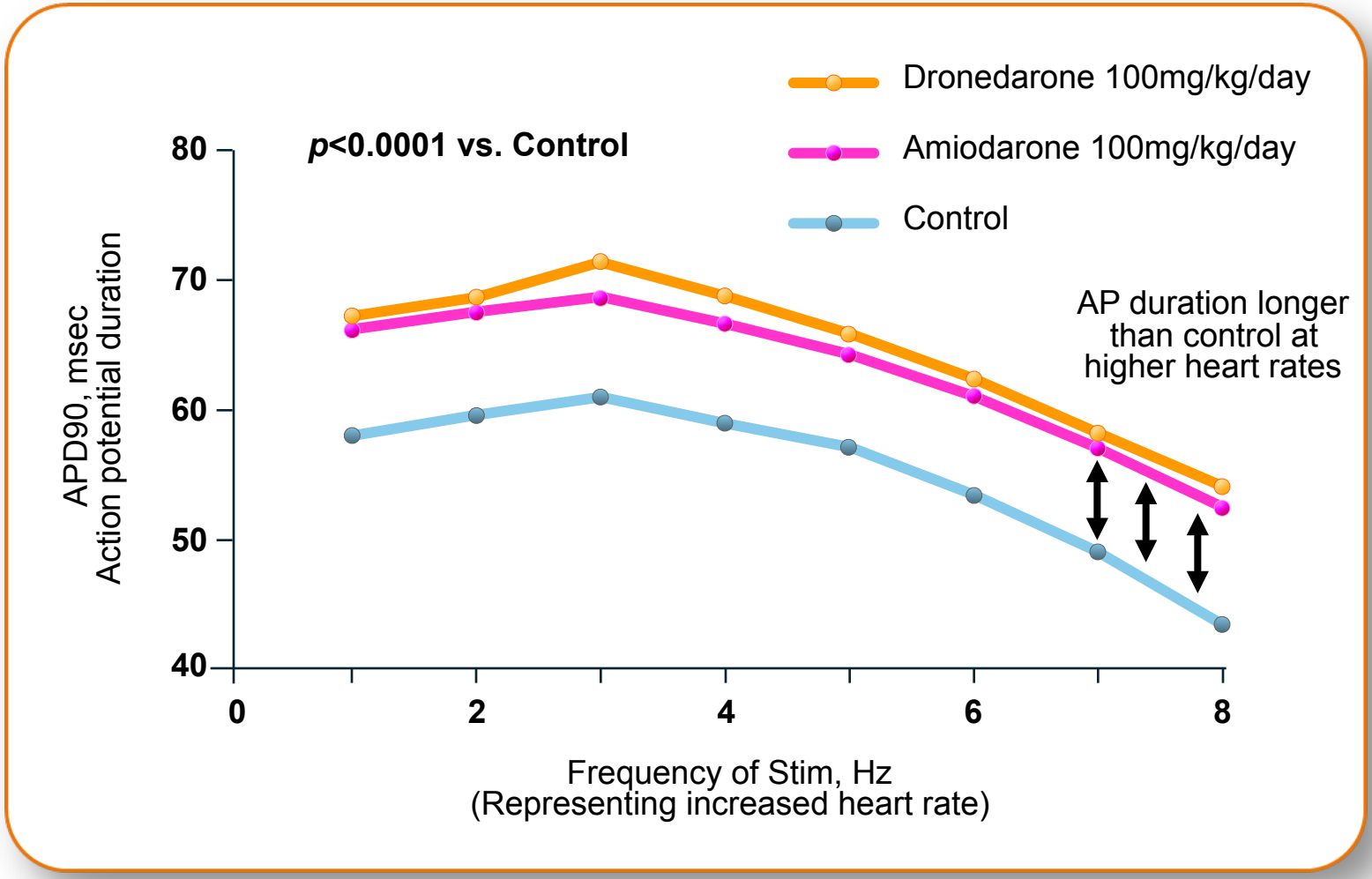


Sicouri S, *et al. J Cardiovasc Pharmacol Ther.* 1997;2:27-38.



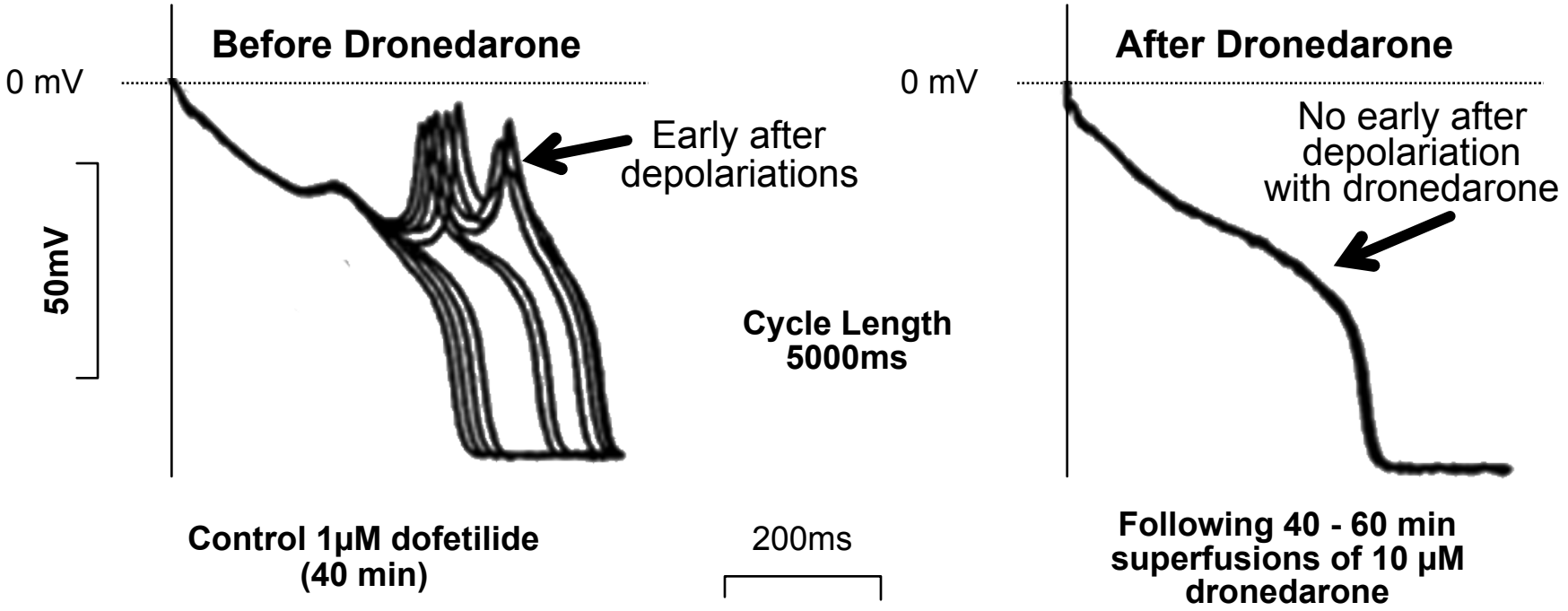
Sicouri S, *Fund Clin Pharmacol.* 1999;13:72.

Dronedarone has a non reverse-use dependent effect on action potential duration



On rabbit atrial APD90 (Action Potential Duration at 90% repolarisation).
Sun W, *et al. J Cardiovasc Pharmacol.* May 2002;39(5):677-684.

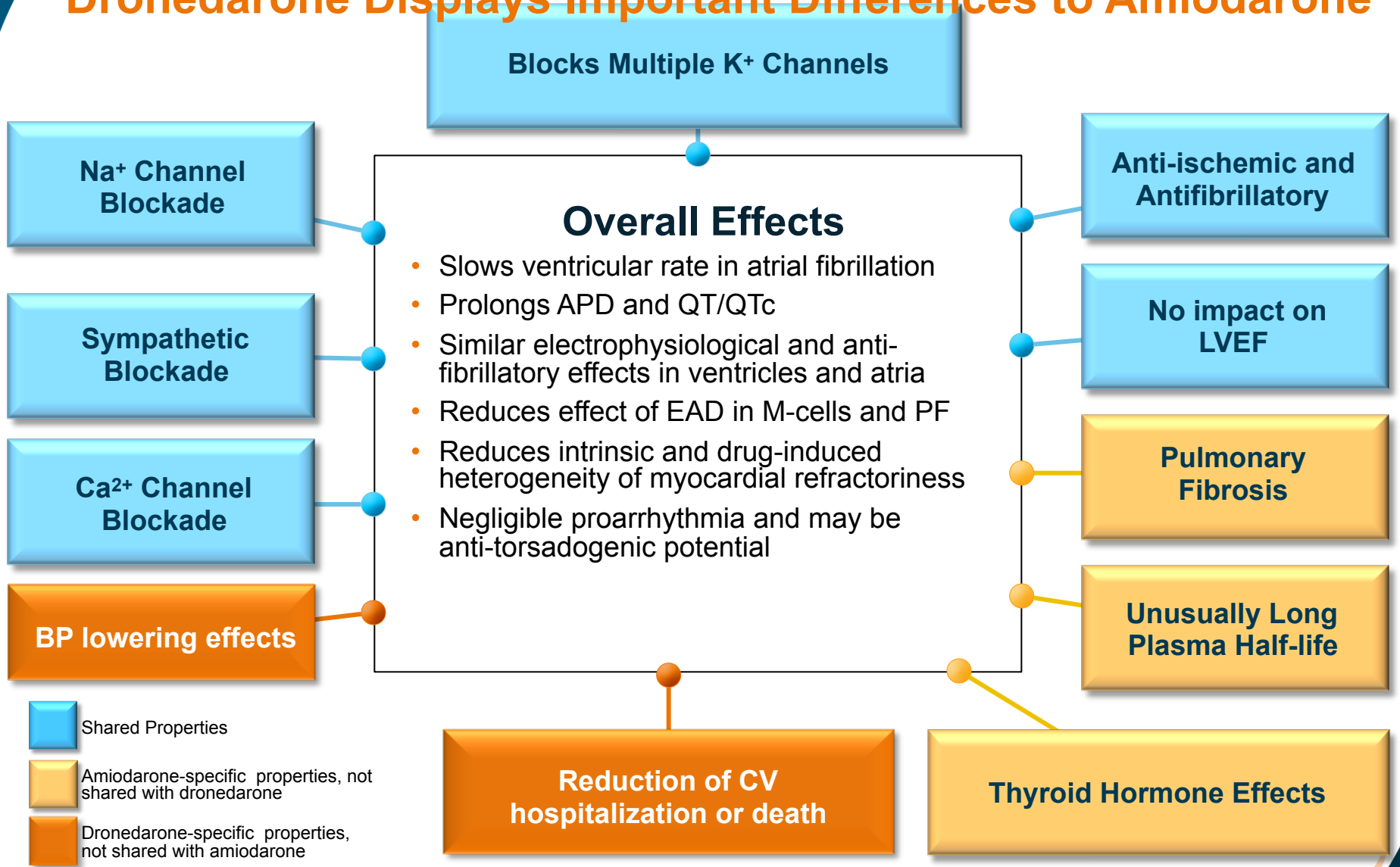
Dronedarone Protects from Early After Depolarisations



EADs induced by Dofetilide in vitro in Dog Purkinje Fibers

Varro A, *et al. Brit J Pharmacol.* 2001;133:625-634.

Dronedarone Displays Important Differences to Amiodarone



Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-26. Hohnloser SH et al. N Engl J Med 2009;360:668-78. Kathofer *et al. Cardiovasc Drug Rev* 2005;23(3):217-30. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM134981.pdf Accessed July 22nd

Dronedarone has Multiple Properties

- Extensive antiarrhythmic efficacy at atrial and ventricular level[1, 2]
- Rate controlling effects[1]
- Vasodilatory effects[2]
- Anti-adrenergic effects[3]
- Blood pressure lowering properties[4]

1 Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
2 Hodeige D, *et al. European Journal of Pharmacology* 1995;279:25-32.
3 Guiraudou P, *et al. European Journal of Pharmacology* 2004;496:119-127.
4 Hohnloser SH et al. N Engl J Med 2009;360:668-78.

Dronedarone background

1a Pharmacology and Mechanism of Action

1b Key safety trials

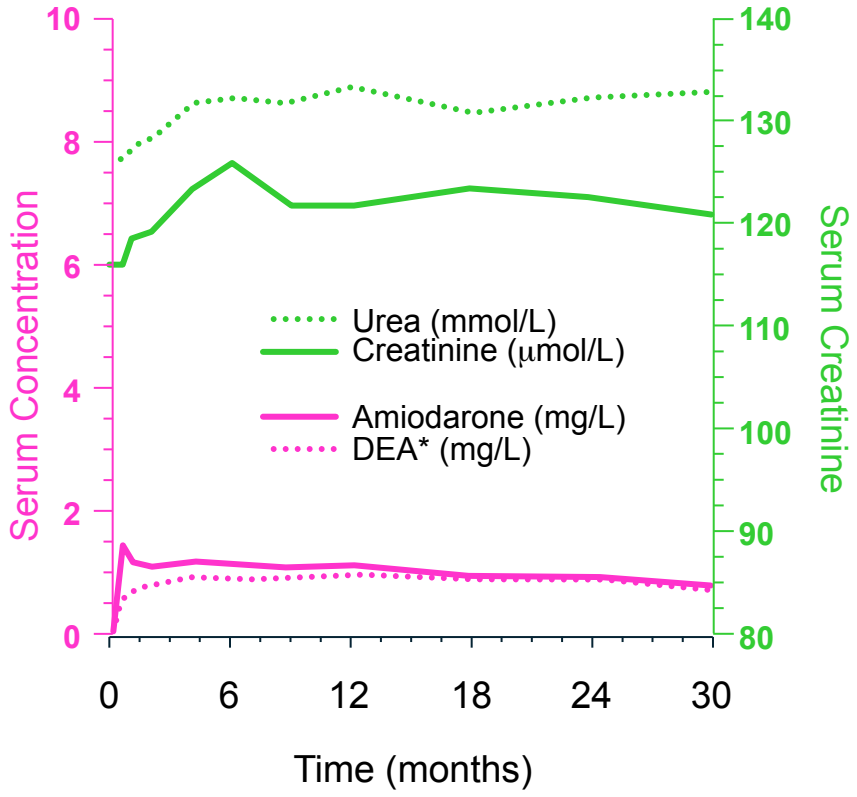
Inhibition of Creatinine Secretion by Dronedarone is Not Indicative of Renal Toxicity

- Study PDY5487 Showed that Dronedarone inhibits the secretion of creatinine at the tubular level in the kidneys, but is not indicative of renal toxicity[1]
- This effect results in mild increase in serum creatinine levels within first 2 weeks of treatment[1]
  - Mean range of serum creatinine increase of 10% to 15%
  - Appears to be fully reversible after dronedarone withdrawal
- Does not interfere with renal function[1]
  - Dronedarone has been proven not to decrease inulin clearance, a reliable marker of renal function
- Dronedarone's effect on creatinine is similar to that seen with amiodarone[2]

1 Tschuppert *et al. Br J Clin Pharmacol.* 2007;64(4):785-91.
2 Pollak P, *Clin Pharma Ther.* 2004;75(2):5.

Amiodarone Effects on Creatinine Levels

- Renal function data in patients receiving amiodarone
  - 30 months duration
  - n=65
- Slow increase in serum creatinine
  - 11% above baseline at 6 months ($p<0.001$)
- Increase in urea
  - 18% above baseline at 12 months ($p<0.001$)
- Decline in uric acid
- No further changes beyond first year of therapy



*Desethylamiodarone

Pollak P. Clin Pharma Ther. 2004;75(2):5
Pollak P. Br J Clin Pharmacol. 1993 Aug;36(2):125-7
Tschuppert et al. Br J Clin Pharmacol. 2007;64(4):785-91

Dronedarone Background Summary

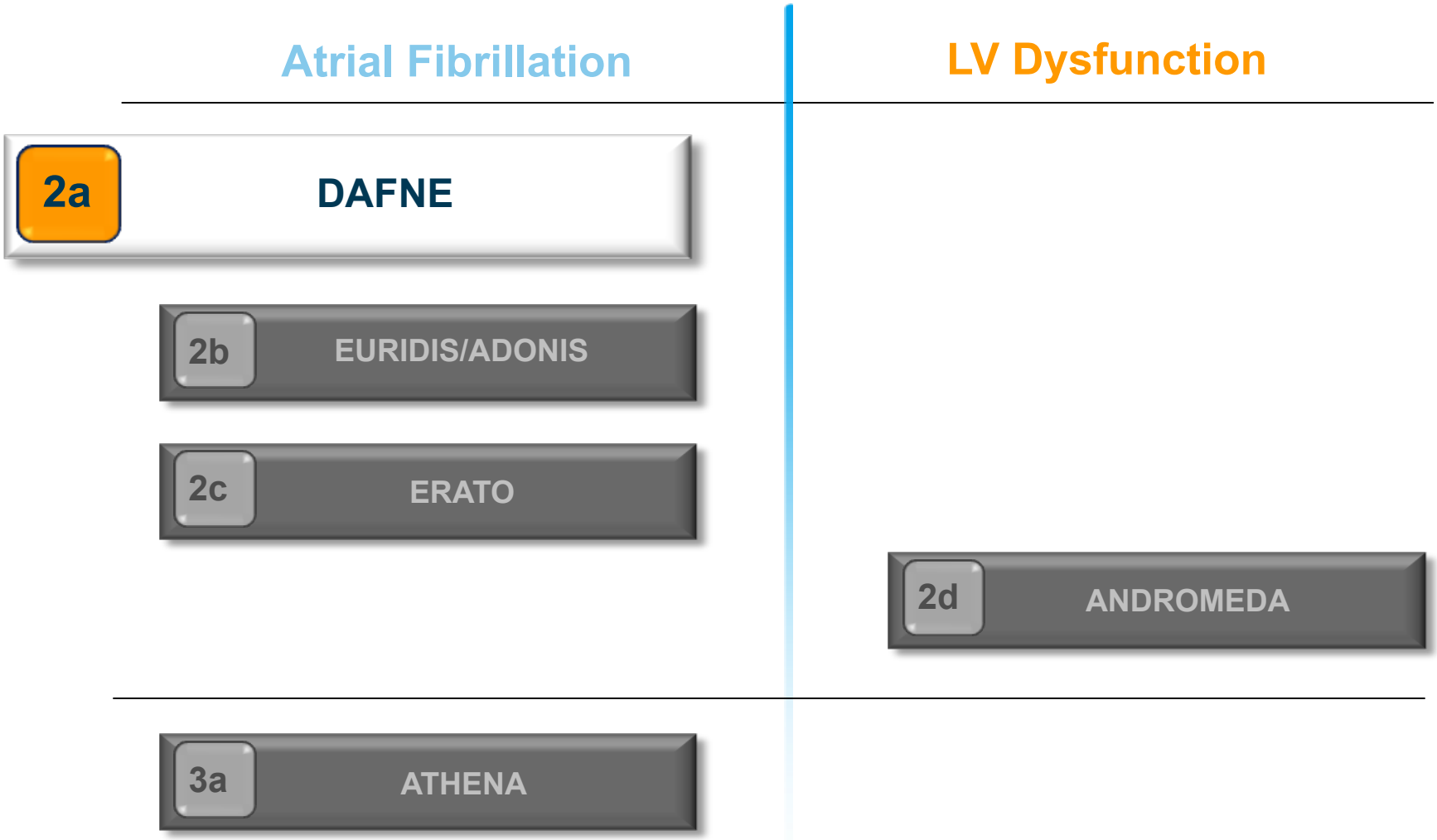
- Dronedarone is a multichannel blocker that possesses electrophysiological characteristics of all four Vaughan Williams classes
- Dronedarone and amiodarone have similar EP profile characterised by a low proarrhythmic effect
- However, dronedarone has key structural differences to amiodarone that may be responsible for its improved clinical profile
- Dronedarone exhibits multiple potentially beneficial properties beyond ion channel inhibition
- Dronedarone inhibits the secretion of creatinine at the tubular level in the kidneys, which is not indicative of renal toxicity

Dronedarone Clinical Trial Programme

Dronedarone Clinical Trial Programme

Atrial Fibrillation	LV Dysfunction
2a DAFNE	
2b EURIDIS/ADONIS	
2c ERATO	
	2d ANDROMEDA
3a ATHENA	

Clinical Trial Programme



DAFNE

Dronedarone **A**trial **F**ibrillatio**N** Study After
Electrical Cardioversion

Objective

- DAFNE aimed to determine the most appropriate dose of dronedarone for preventing recurrence of AF after cardioversion in patients with persistent AF

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Study Endpoints

- Primary endpoint
  - Time to first AF recurrence (episode lasting for at least 10 min and documented by two distinct ECGs)
- Secondary study endpoints
  - Spontaneous conversion of AF following randomisation
  - Heart rate in case of AF recurrence
  - Incidence of side effects

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Inclusion and Exclusion Criteria

Inclusion criteria

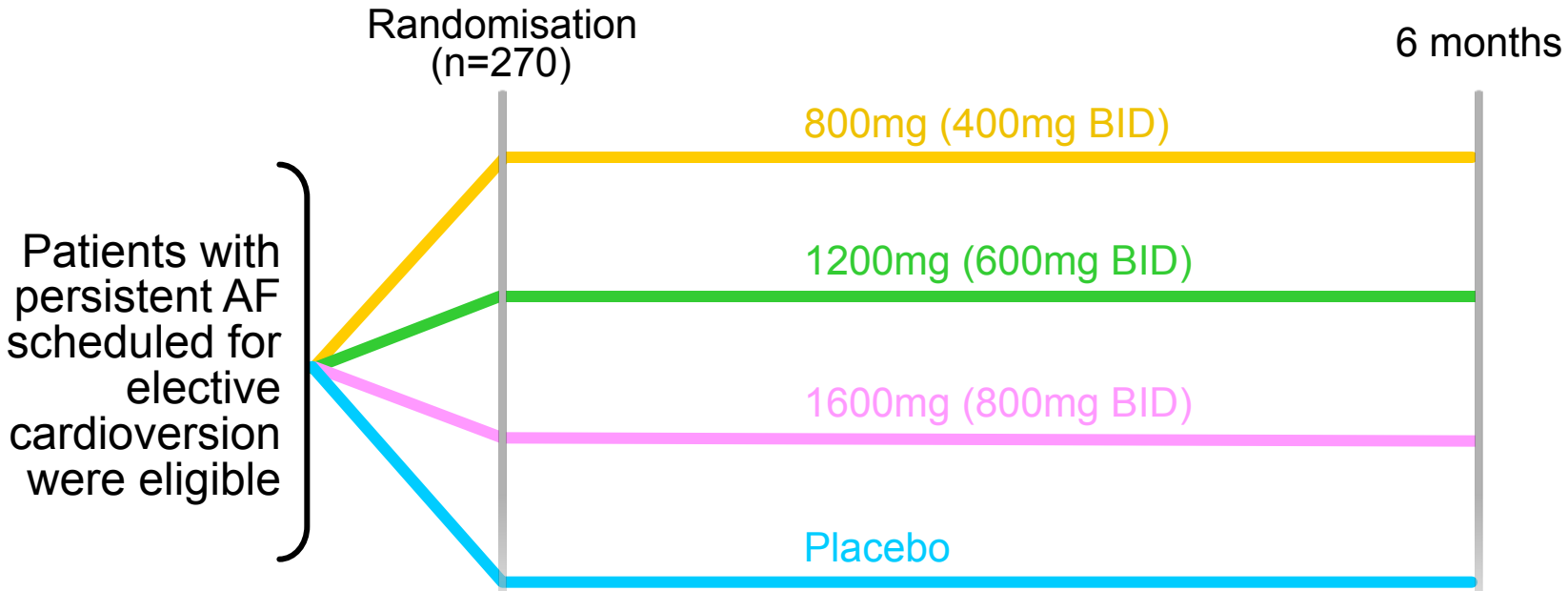
- Men & women aged 21-85 years
- Persistent AF (between 72h and 12 months duration)
- AF could be lone or associated with ischemic or hypertensive heart disease or dilated cardiomyopathy
- Coexisting valvular anomaly did not preclude inclusion except for those patients with hemodynamically significant dysfunction at echocardiography

Exclusion criteria

- >2 cardioversions in the last six months
- Acute reversible cause
- Atrial flutter as the presenting arrhythmia
- Unstable angina pectoris or recent myocardial infarction
- QT interval >500 msec, or history of torsades de pointes
- Severe bradycardia
- Advanced atrioventricular block
- Treatment with other antiarrhythmic drugs
- Congestive heart failure class III or IV
- Left ventricular ejection fraction <35%
- Wolff-Parkinson-White syndrome
- Implanted cardioverter defibrillator

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Study design



- If sinus rhythm was not restored after drug exposure for 5-7 days, electrical cardioversion was carried out
- Successfully cardioverted patients continued treatment for 6 months

- A prospective, randomised study conducted in 50 centres in 11 countries

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

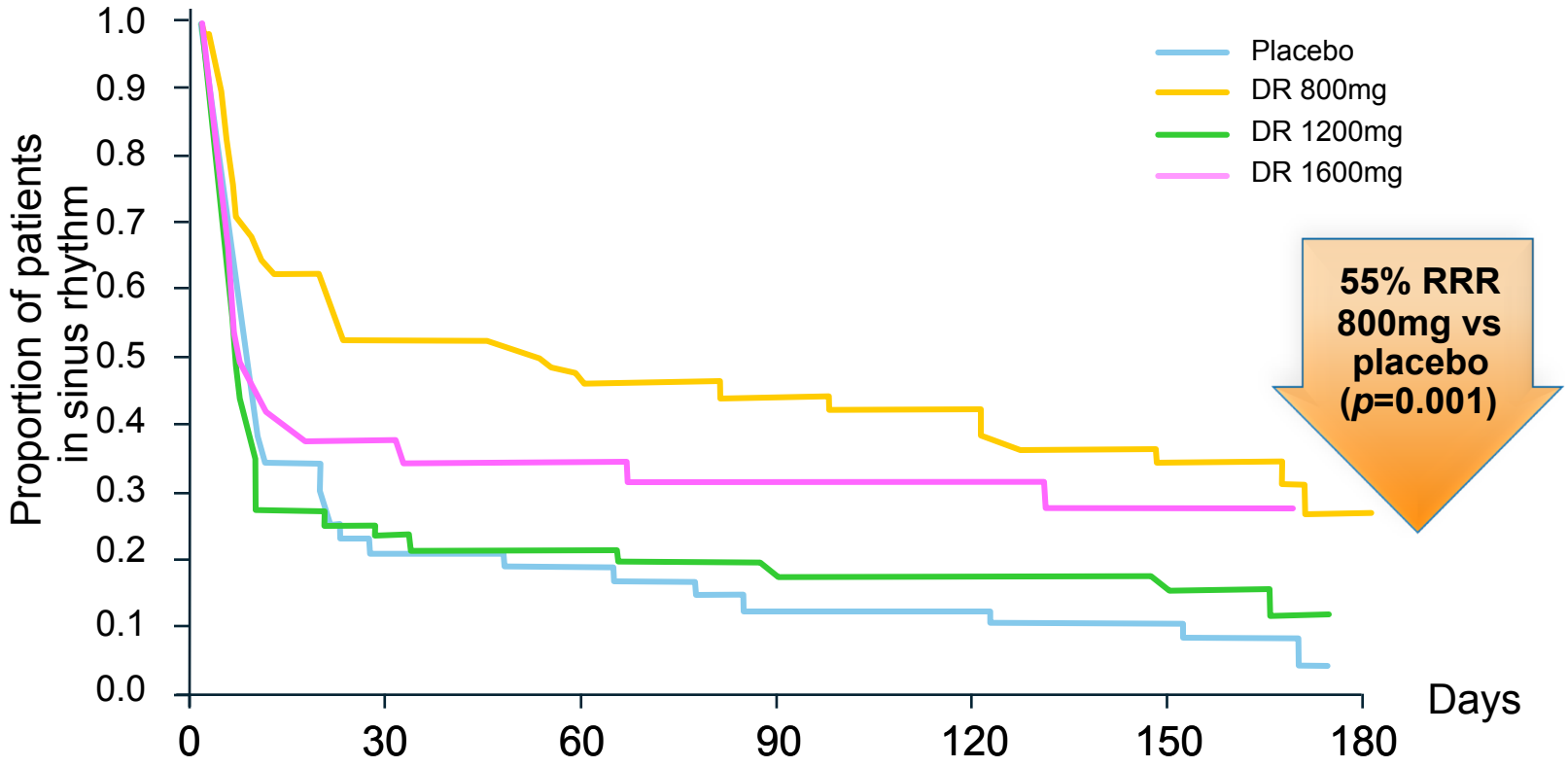
Baseline Patient Characteristics

	Placebo n=48	DR 800mg n=54	DR 1200mg n=54	DR 1600mg n=43
Age (years)	65	64	63	62
Male sex (%)	79	57	70	67
Hypertension (%)	56	51	50	44
CAD[1]	27	20	18	20
Valve disease (%)	50	35	31	37
Heart Failure (%)	22	14	24	11
AF[2] duration (days)	82	122	92	108
Recurrent AF[2] (%)	65	50	64	54
LA[3] size (mm)	46	44	45	45
LVEF[4] (%)	56	55	53	54

Touboul P, *et al. Eur Heart J*. 2003;24:1481-7.

1 CAD: Coronary Artery Disease
2 AF: Atrial Fibrillation
3 LA: Left Atrium
4 LVEF: Left Ventricular Ejection Fraction

Dronedarone 400mg bid Significantly Prolonged Time to First AF Recurrence



n exp.

Placebo	48	12	11	8	8	7	5
DR 800mg	54	29	26	25	24	21	18
DR 1200mg	54	14	13	12	11	11	9
DR 1600mg	43	15	12	11	11	9	8

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Dronedarone 400mg bid was Well-Tolerated with No Incidence of Proarrhythmic Events and No Evidence of Organ Toxicity

Adverse Events leading to drug discontinuation	Placebo n=66	DR 800mg n=76	DR 1200mg n=66	DR 1600mg n=62	Dronedarone n=204
Total	0 (0.0)	3 (3.9)	5 (7.6)	14 (22.6)	22 (10.8)
Gastrointestinal[1]	0 (0.0)	1 (1.3)	1 (1.5)	7 (11.3)	9 (4.4)
General disorders[2]	0 (0.0)	0 (0.0)	1 (1.5)	4 (6.5)	5 (2.5)
Cardiac failure	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.6)	2 (1.0)
Central Nervous System (dizziness)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.6)	2 (1.0)
Dermatology	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.6)	2 (1.0)
Extrasystoles	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
QT increase	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Tachycardia supraventricular	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Thrombosis	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)

1 Gastrointestinal disorders include diarrhea, vomiting, nausea and gastroenteritis.
2 General disorders include malaise, accidental injury, anaphylactic shock and weight decrease.

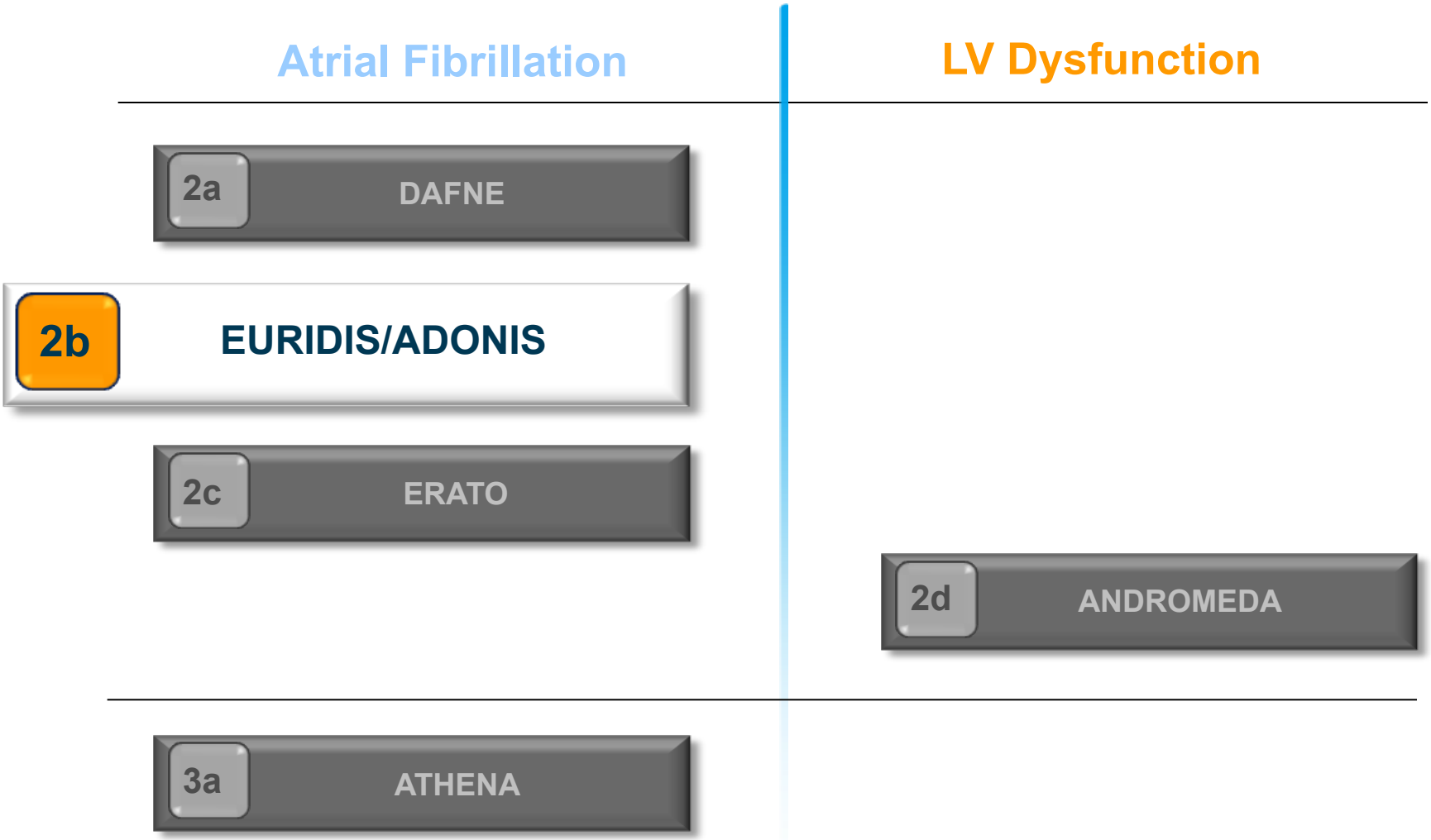
Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Conclusions

- DAFNE was the first prospective randomised trial to evaluate the efficacy and safety of dronedarone in patients undergoing cardioversion for persistent AF
- The results demonstrated that dronedarone at a dose of 400mg bid significantly increases the time to first AF recurrence when compared to placebo
- At this dose, the drug was well tolerated and proved to be safe during short-term exposure
  - No thyroid abnormalities
  - No proarrhythmia
- Based on these promising results, dronedarone 400mg bid was chosen to be further explored in the phase III EURIDIS/ADONIS trials

Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.

Clinical Trial Programme



EURIDIS

EURopean Trial **I**n Atrial Fibrillation or Flutter Patients Receiving **D**ronedarone for the Ma**I**ntenance of **S**inus Rhythm

ADONIS

American-Australian-African Trial with **D**ronedar**ON**e **I**n Atrial Fibrillation or Flutter Patients for the Maintenance of **S**inus Rhythm

Objective

- EURIDIS and ADONIS investigated whether dronedarone is superior to placebo on top of standard therapy* for maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from atrial fibrillation or atrial flutter

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins

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

Study Endpoints

- Primary endpoint
  - Time to first AF/AFL recurrence
    - Episode lasting at least 10 minutes and confirmed by two consecutive recordings taken 10 minutes apart on 12-lead ECG or transtelephonic monitoring
- Secondary endpoints
  - Symptoms related to atrial fibrillation during recordings of 12-lead ECG or transtelephonic monitoring
  - Mean ventricular rate during the first recurrence of AF/AFL

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

Inclusion and Exclusion Criteria

Inclusion criteria

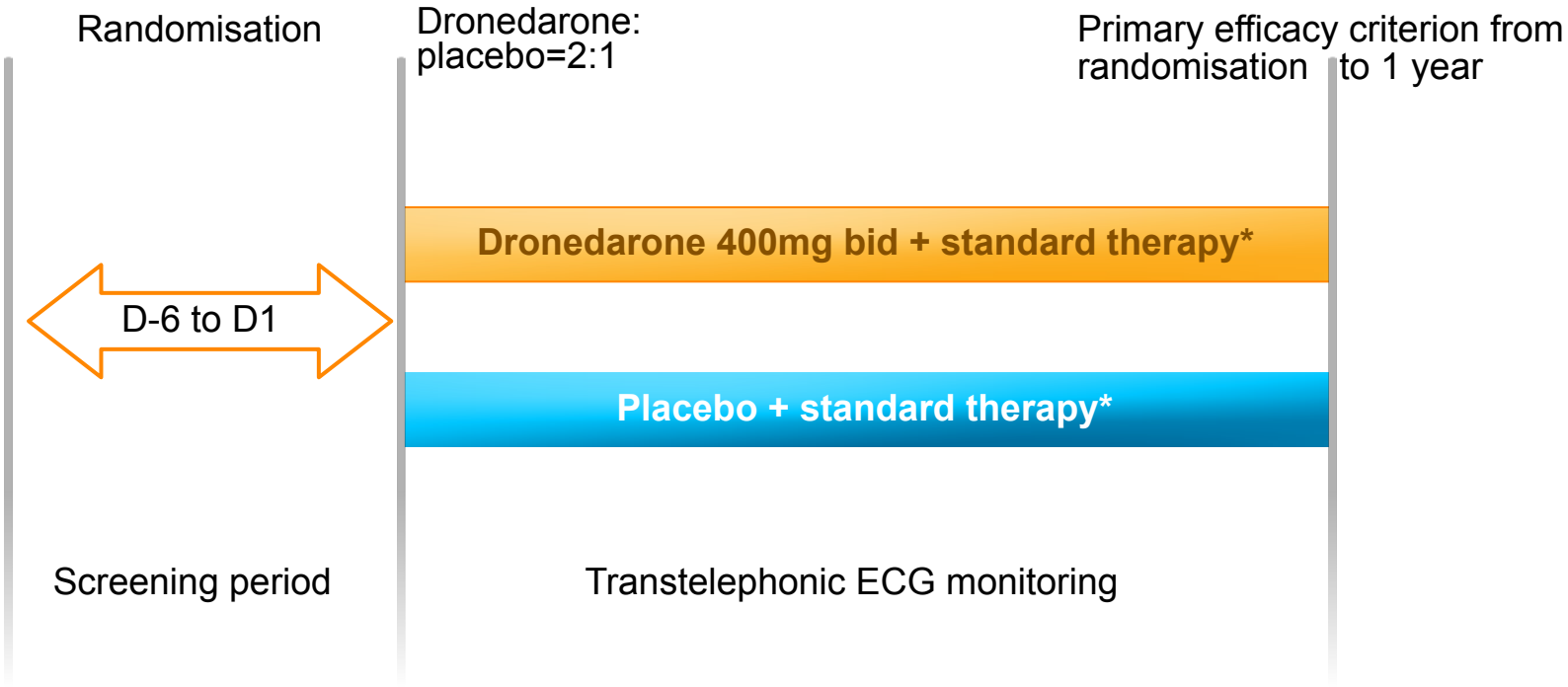
- Men & women
- Aged ≥21 years
- In sinus rhythm for at least 1 hour at time of randomisation
- Paroxysmal or persistent AF (At least one ECG–documented AF/ AFL episode in last 3 months)

Exclusion criteria

- Permanent atrial fibrillation (i.e., a duration of at least 12 months)
- Patients who had had torsades de pointes
- Patients with persistent bradycardia of less than 50 beats per minute
- Patients with a PR interval of 0.28 second or more
- Second degree (or higher) atrioventricular block
- Patients who were taking class I or III antiarrhythmic agents
- Patients with NYHA class III or IV CHF

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

Study Design



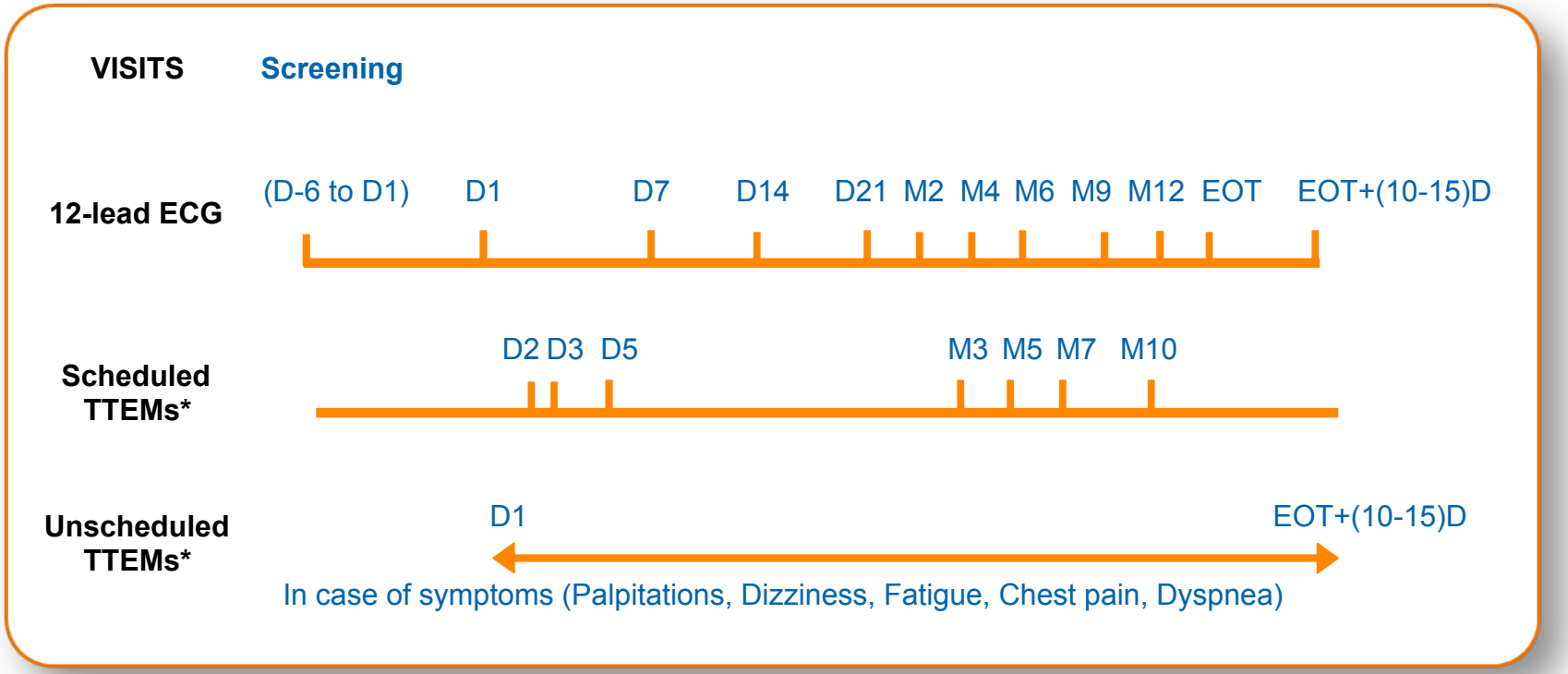
- The EURIDIS trial was carried out in 12 European countries, involving 80 clinical trial study sites
- ADONIS was carried out in 115 centres in 5 countries across 4 continents

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Monitoring of AF/AFL Recurrence was Highly Sensitive

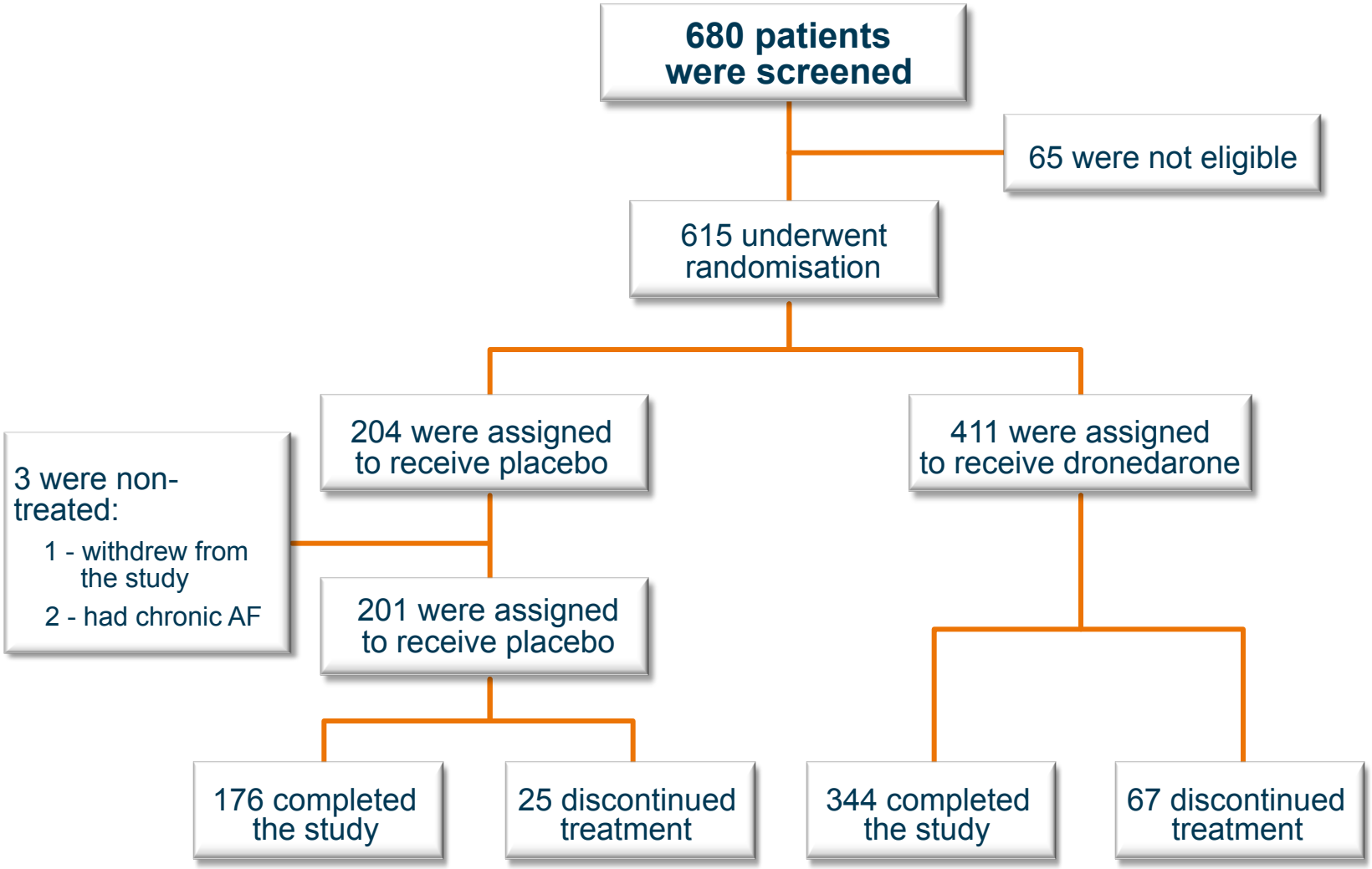
- TTEM* recording was performed in addition to 12-lead ECG to detect recurrence of atrial fibrillation or atrial flutter at study endpoint



* TTEM=Trans Telephonic Electrocardiogram Monitoring.

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

EURIDIS Study Flow Chart



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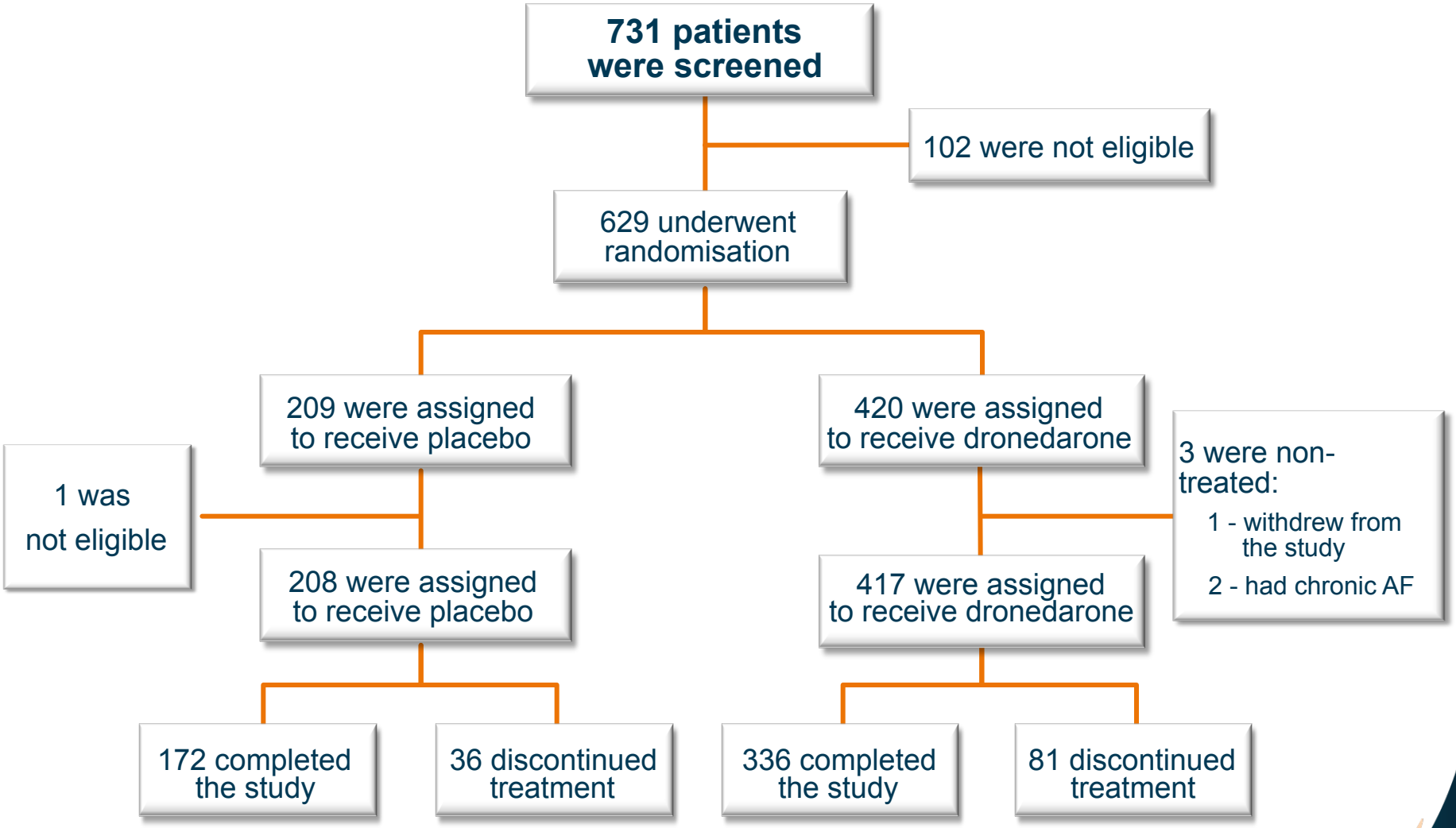
ADONIS Study Flow Chart



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

EURIDIS ADONIS

Baseline Patient Characteristics

Characteristic	EURIDIS European Trial		ADONIS Non-European Trial		EURIDIS/ADONIS Combined Trials	
	Placebo n=201	Dronedarone n=411	Placebo n=208	Dronedarone n=417	Placebo n=409	Dronedarone n=828
Sex - no. (%)						
Female	61 (30.3)	126 (30.7)	68 (32.7)	124 (29.7)	129 (31.5)	250 (30.2)
Male	140 (69.67)	285 (69.3)	140 (67.3)	293 (70.3)	280 (68.5)	578 (69.8)
Age (years)	61.3 ±10.7	62.3 ±10	63 ±11.4	64.6 ±11.3	62.2 ±11.1	63.5 ±10.7
Body Mass Index - no. (%)						
<30	143 (73.3)	287 (70.9)	130 (63.7)	251 (61.2)	273 (68.4)	538 (66.0)
≥30	52 (26.7)	118 (29.1)	74 (36.3)	159 (38.8)	126 (31.6)	277 (34.0)
Weight (kg)	86.43 ±14.78	83.84 ±14.4	87.81 ±19.3	88.61 ±19.9	87.14 ±17.2	86.25 ±17.5

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

Cardiovascular History of Patients

Characteristic	EURIDIS European Trial		ADONIS Non-European Trial		EURIDIS/ADONIS Combined Trials	
	Placebo n=201	Dronedarone n=411	Placebo n=208	Dronedarone n=417	Placebo n=409	Dronedarone n=828
Structural heart disease	65 (33.3)	149 (36.3)	94 (45.6)	199 (48.5)	159 (39.7)	348 (42.4)
Hypertension	108 (53.7)	255 (62.0)	97 (46.6)	242 (58.0)	205 (50.1)	497 (60.0)
Coronary artery disease	31 (15.4)	91 (22.1)	44 (21.2)	104 (24.9)	75 (18.3)	195 (23.6)
Clinically relevant valvular heart disease	19 (9.5)	50 (12.2)	42 (20.2)	86 (20.6)	61 (14.9)	136 (16.4)
Non-ischemic cardiomyopathy	11 (5.5)	16 (3.9)	19 (9.1)	34 (8.2)	30 (7.3)	50 (6.0)
Hypertrophic cardiomyopathy	8 (4.0)	10 (2.4)	4 (1.9)	13 (3.1)	12 (2.9)	23 (2.8)
Rheumatic heart disease	6 (3.0)	7 (1.7)	8 (3.8)	18 (4.3)	14 (4.3)	25 (3.0)
Congenital heart disease	2 (1.0)	9 (2.2)	1 (0.5)	4 (1.0)	3 (0.7)	13 (1.6)
Implanted Pacemaker	7 (3.5)	33 (8.0)	13 (6.2)	31 (7.4)	20 (4.9)	64 (7.7)
ICD	3 (1.5)	0	2 (1.0)	6 (1.4)	5 (1.2)	6 (0.7)

ICD=Implanted Cardioverter-Defibrillator.

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

CHF History

Characteristic	EURIDIS European Trial		ADONIS Non-European Trial		EURIDIS/ADONIS Combined Trials	
	Placebo n=201	Dronedarone n=411	Placebo n=208	Dronedarone n=417	Placebo n=409	Dronedarone n=828
Left ventricular ejection fraction - %						
	59.83 ±9.4	59.57 ±10.2	57.21 ±12.2	57.91 ±11.2	58.5 ±11.0	58.75 ±10.8
Left atrial anteroposterior diameter - mm						
	42.7 ±6.7	42.4 ±6.6	42.0 ±6.9	42.9 ±7.4	42.4 ±6.8	42.6 ±7.0
Congestive Heart Failure - no. (%)						
Any disease	37 (18.4)	65 (15.8)	36 (17.3)	78 (18.7)	73 (17.8)	143 (17.3)
NYHA class I	16 (8.0)	19 (4.6)	10 (4.8)	28 (6.7)	26 (6.4)	47 (5.7)
NYHA class II	21 (10.4)	46 (11.2)	26 (12.5)	50 (12.0)	47 (11.5)	96 (11.6)

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

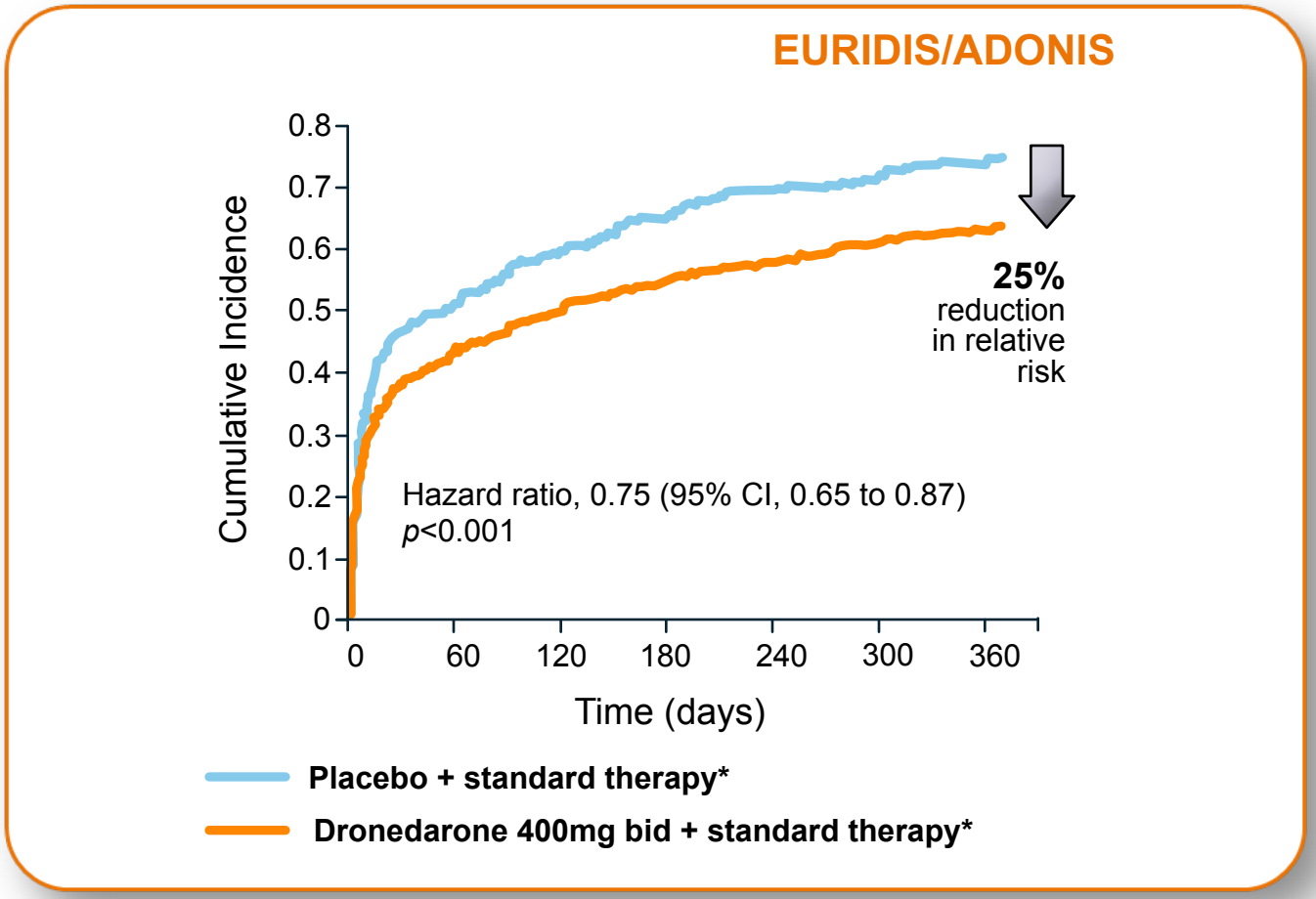
EURIDIS ADONIS

Concomitant Medications

Characteristic	EURIDIS European Trial		ADONIS Non-European Trial		EURIDIS/ADONIS Combined Trials	
	Placebo n=201	Dronedarone n=411	Placebo n=208	Dronedarone n=417	Placebo n=409	Dronedarone n=828
Concomitant cardiovascular therapy no. (%)						
Digoxin	42 (20.9)	51 (12.4)	53 (25.5)	94 (22.5)	95 (23.2)	145 (17.5)
Calcium channel blocker (rate lowering)	23 (11.4)	36 (8.8)	55 (26.4)	103 (24.7)	78 (19.1)	139 (16.8)
Beta-blocker (except sotalol)	124 (61.7)	245 (59.6)	114 (54.8)	208 (49.9)	238 (58.2)	453 (54.7)
Oral anticoagulant	142 (70.6)	273 (66.4)	149 (71.6)	298 (71.5)	291 (71.1)	571 (69.0)
Long term antiplatelet therapy	64 (31.8)	135 (32.8)	88 (42.3)	191 (45.8)	152 (37.2)	326 (39.4)
Statin	52 (25.9)	95 (23.1)	79 (38.0)	168 (40.3)	131 (32.0)	263 (31.8)
ACE inhibitor	79 (39.3)	176 (42.8)	80 (38.5)	151 (36.2)	159 (38.9)	327 (39.5)

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

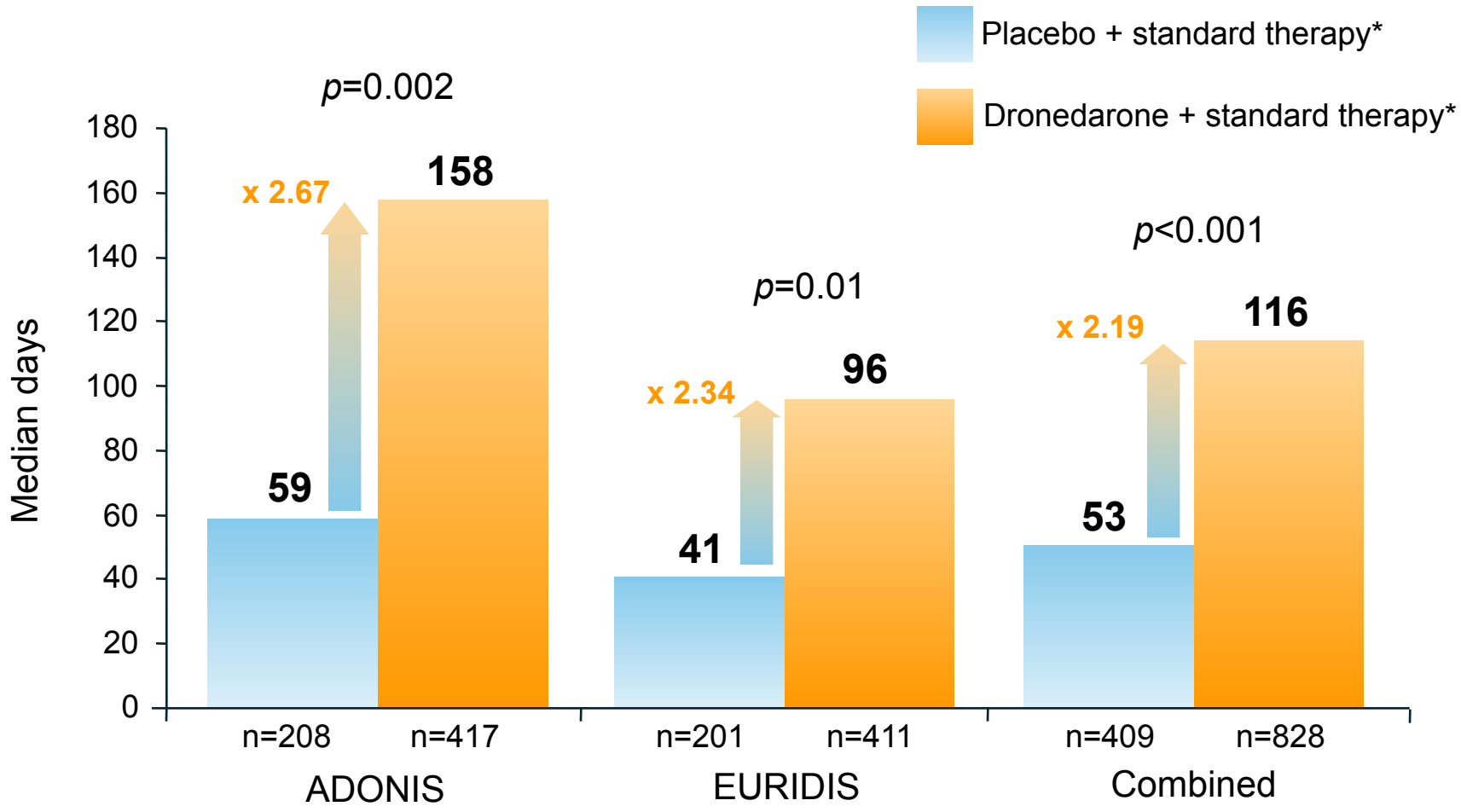
Dronedarone Showed a Significant Reduction in First AF Recurrence in the Combined Analysis



*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Dronedarone More Than Doubled Time to First Recurrence of AF/AFL



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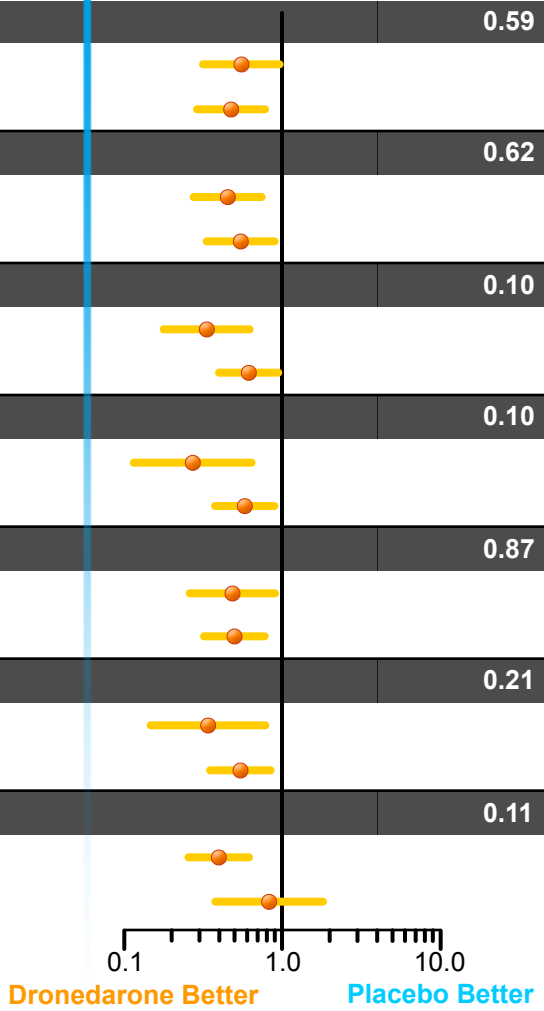
Singh BN, *et al. N Engl J Med.* 2007;357:987-99.

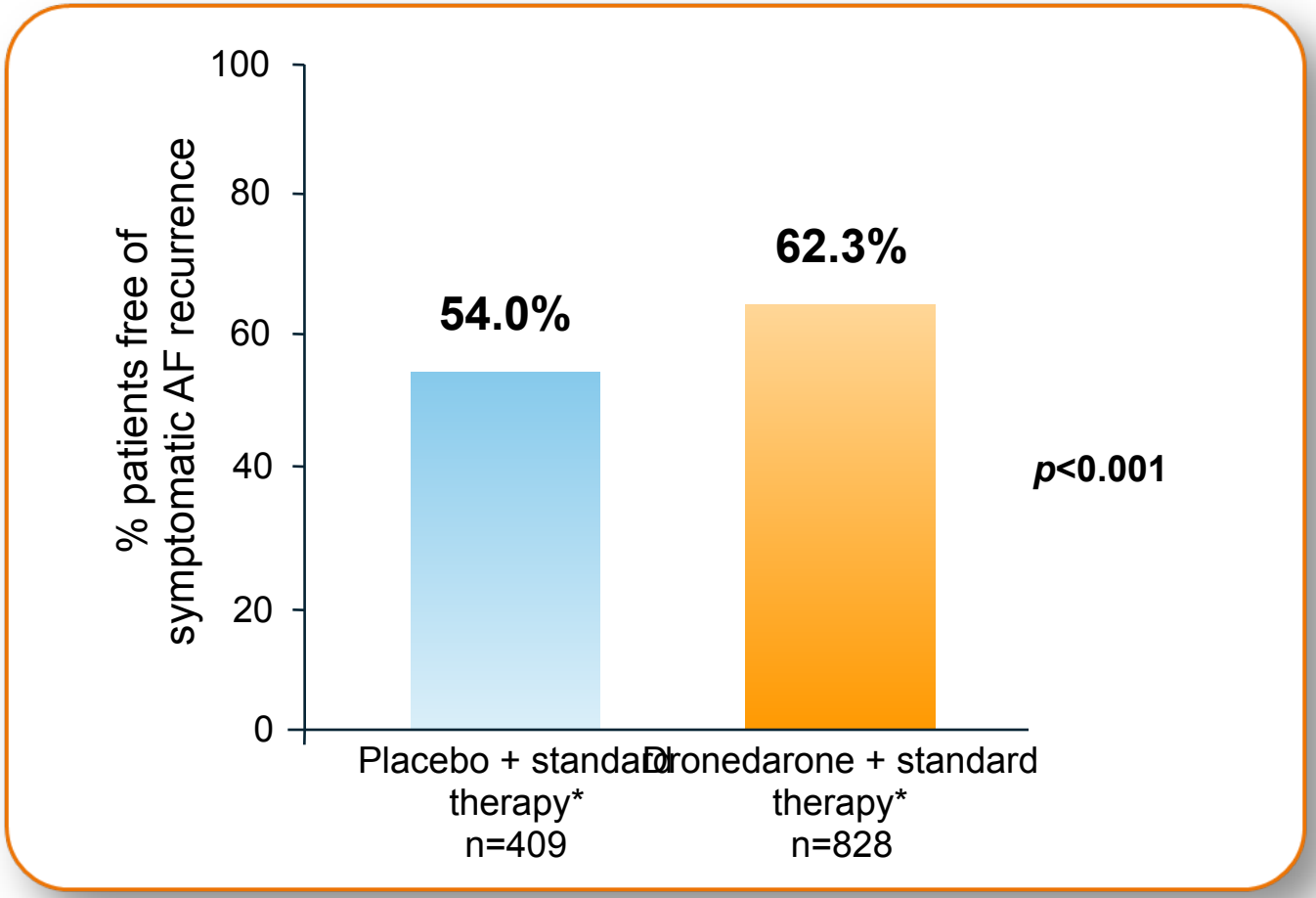
Dronedarone Reduced Recurrence of AF/AFL Across Clinically Relevant Patient Subgroups

Subgroup	No. of Patients	Hazard Ratio for Event (95% CI)	*p* value for interaction
Structural heart disease			**0.59**
Yes	507	0.79 (0.63-0.99)	
No	714	0.74 (0.62-0.89)	
Hypertension			**0.62**
Yes	702	0.73 (0.60-0.89)	
No	535	0.79 (0.64-0.97)	
Left atrial diameter			**0.10**
≤40 mm	465	0.65 (0.51-0.82)	
>40 mm	735	0.83 (0.69-0.99)	
Heart failure criteria met			**0.10**
Yes	216	0.59 (0.42-0.83)	
No	946	0.81 (0.69-0.95)	
Conversion to sinus rhythm in ≤5 days			**0.87**
Yes	364	0.76 (0.59-0.97)	
No	873	0.76 (0.64-0.90)	
Previous use of amiodarone			**0.21**
Yes	223	0.60 (0.43-0.84)	
No	1014	0.79 (0.67-0.92)	
Previous use of antiarrhythmic drugs			**0.11**
Yes	903	0.70 (0.59-0.82)	
No	334	0.92 (0.68-1.25)	



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

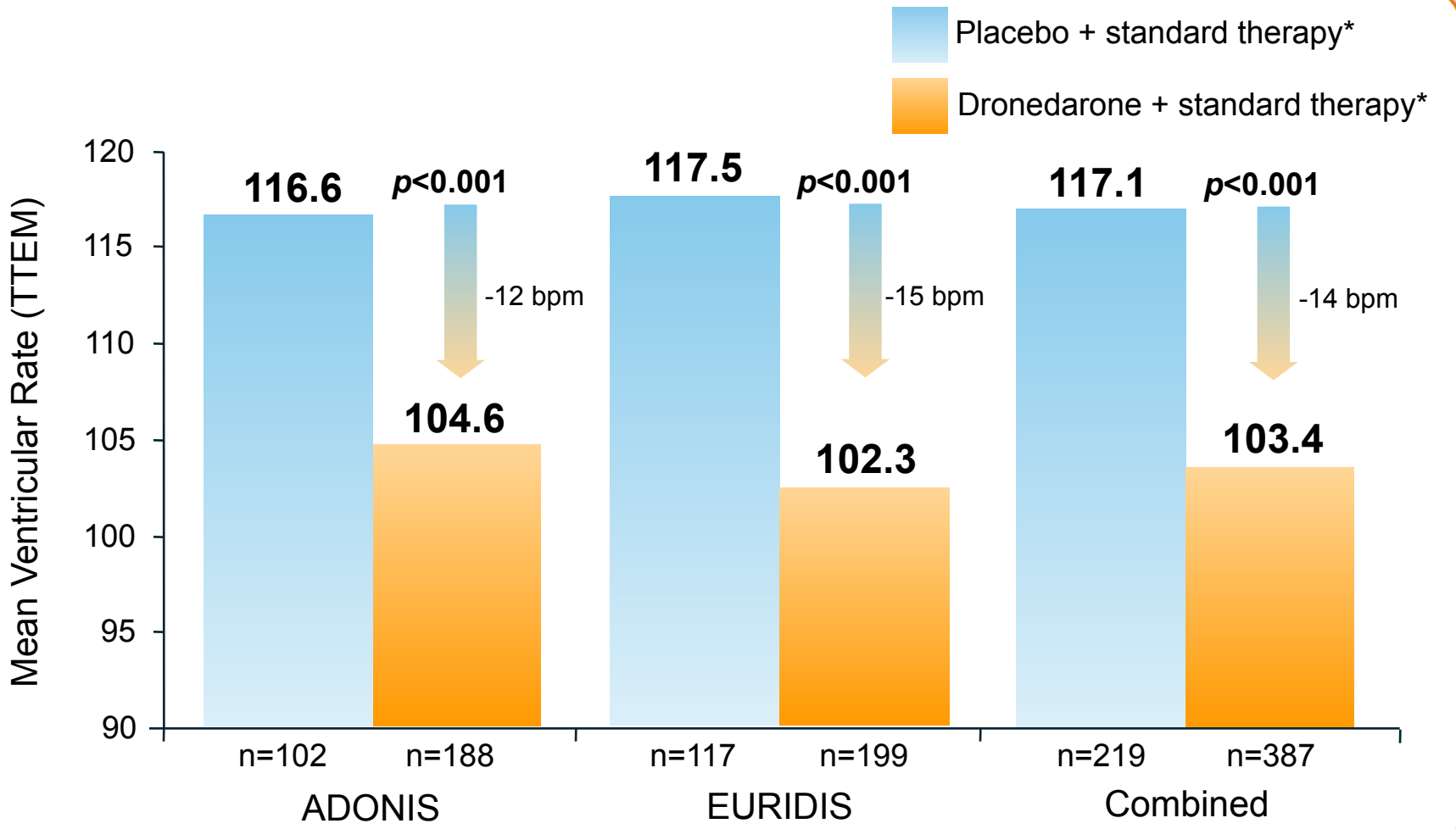
More than 6 in 10 Patients on Dronedarone were Free of Symptomatic AF Recurrence at 1 Year



*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Dronedarone Showed a Significant and Consistent Decrease in Ventricular Rate at First AF/AFL Recurrence



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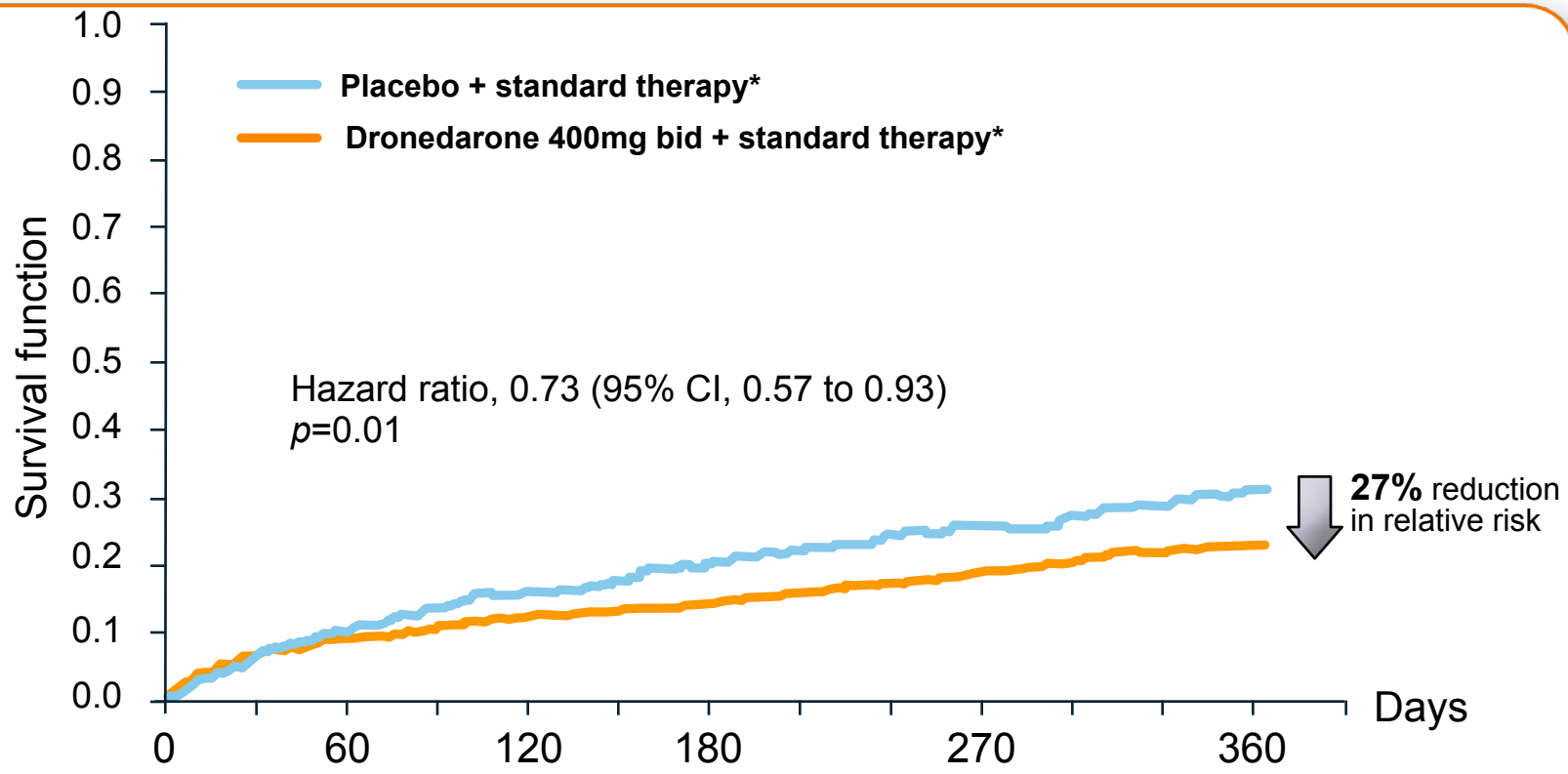
TTEM=Trans Telephonic Electrocardiogram Monitoring.

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

EURIDIS
ADONIS

Post-hoc Analysis showed that Dronedarone Significantly Reduced Relative Risk of First All-cause Hospitalisation or Death by 27%



Patients at risk:

Placebo	409	320	272	241	205	179
DR 400mg	828	668	597	559	494	440

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

Data on file.

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

Adverse Events Rates with Dronedarone were Similar to Placebo

Event	Placebo n=409	Dronedarone n=828	*p* value
Death - no. (%)			
Any cause	3 (0.7)	8 (1.0)	1.00
Sudden death	1 (0.2)	4 (0.5)	1.00
Pulmonary event - no. (%)			
Cough	7 (1.7)	19 (2.3)	0.67
Dyspnea	15 (3.7)	27 (3.3)	0.74
Endocrine event - no./total no. (%)			
Hyperthyroidism	56/396 (14.1)	67/801 (8.4)	0.002
Hypothyroidism	14/396 (3.5)	44/801 (5.5)	0.15
Cardiac event - no. (%)			
Bradycardia or conduction block (any)	8 (2.0)	22 (2.7)	0.56
Bradycardia or conduction block (serious)	3 (0.7)	8 (1.0)	1.00
Heart failure or shock (any)	4 (1.0)	20 (2.4)	0.12
Heart failure or shock (serious)	3 (0.7)	13 (1.6)	0.29
Gastrointestinal			
Diarrhea	20 (4.9)	59 (7.1)	0.14
Nausea	14 (3.4)	36 (4.3)	0.54
Elevation of serum creatinine	1 (0.2)	20 (2.4)	0.004

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

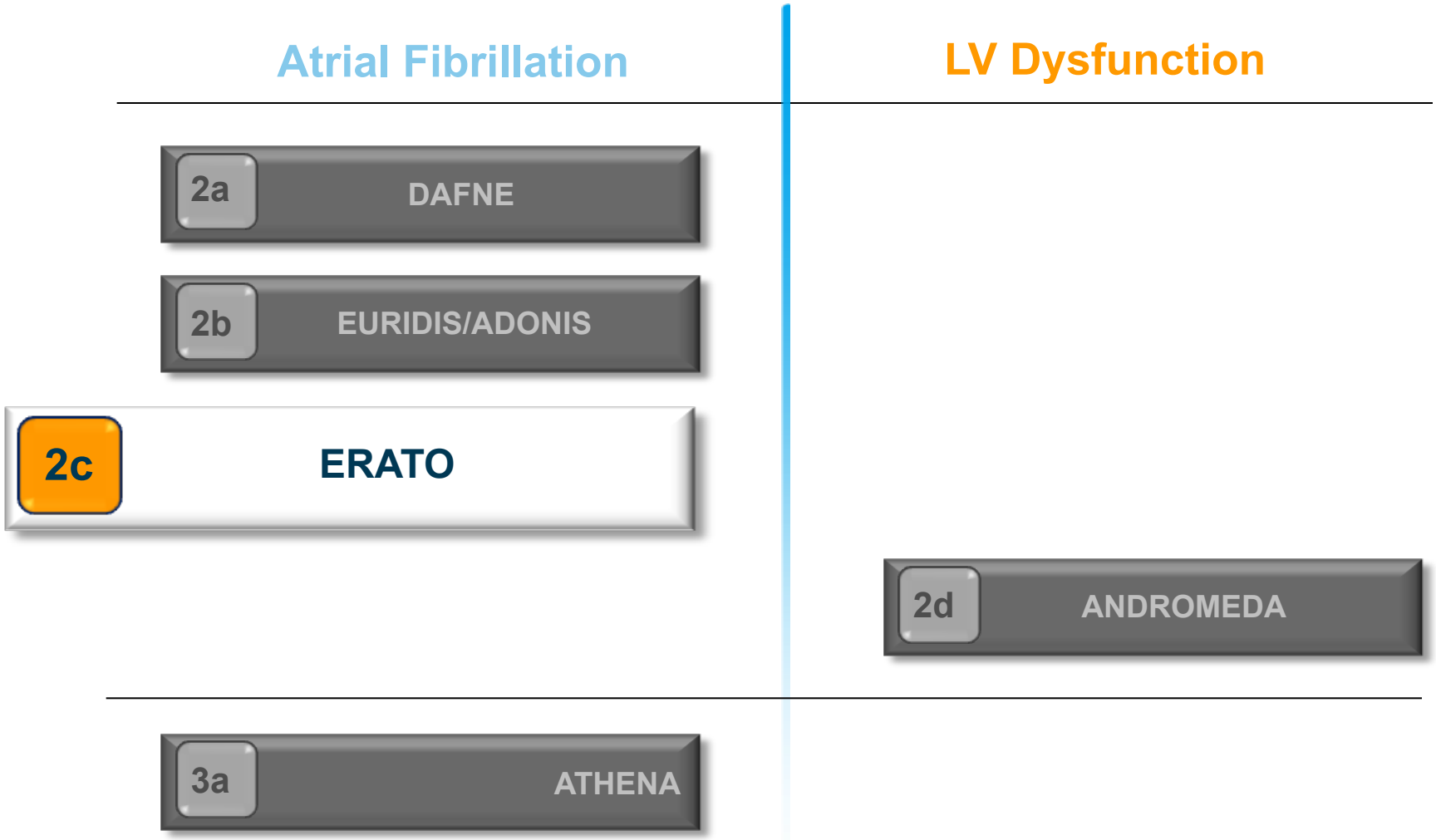
EURIDIS
ADONIS

Conclusions

- Both the EURIDIS and ADONIS trials consistently showed that dronedarone was significantly more effective than placebo on top of standard therapy at prolonging the time to first symptomatic and asymptomatic recurrence in patients with paroxysmal or persistent AF
- In addition to this rhythm control effect, dronedarone demonstrated a significant decrease in ventricular rate during first AF recurrence
- Dronedarone was well-tolerated with a similar safety profile to placebo:
  - No reported torsades de pointes
  - No evidence of organ toxicity (thyroid, pulmonary, hepatic, etc)
  - No excess of worsening CHF
- Furthermore, pooled post-hoc analysis showed a significant reduction in all-cause hospitalisation or death relative to placebo

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

Clinical Trial Programme



ERATO

Efficacy and Safety of DRonedArone for The COntrol of Ventricular Rate during Atrial Fibrillation study

Objectives

- Primary objective
  - To assess the efficacy of dronedarone in the control of mean 24-hour ventricular rate in patients with permanent AF when added to standard therapy*
- Secondary objectives
  - Assessment of the effects of dronedarone on heart rate during exercise
  - The impact of treatment on exercise tolerance, and the tolerability of dronedarone

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Study endpoints

- Primary endpoint
  - Change in mean ventricular rate measured by 24-hour Holter on Day 14 compared to baseline
- Secondary endpoints
  - Change in ventricular rate during submaximal and maximal symptom-limited exercise test on D14 (or D15) compared to baseline D0 (or D1) without decrease in exercise performance
  - Change in maximal exercise duration at D14 compared with D0
  - Change in mean ventricular rate measured by 24-hour Holter at 4 months compared to baseline

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

Inclusion and Exclusion criteria

Inclusion criteria

- Patients of either sex
- Aged ≥21 years
- With symptomatic* permanent AF (defined as AF lasting >6 months) for which cardioversion is not considered
- With resting ventricular rate ≥80 beats per minute at screening measured on a 6-second rhythm strip
- Receiving standard therapy (betablockers, CCB, digitalis etc)

Exclusion criteria

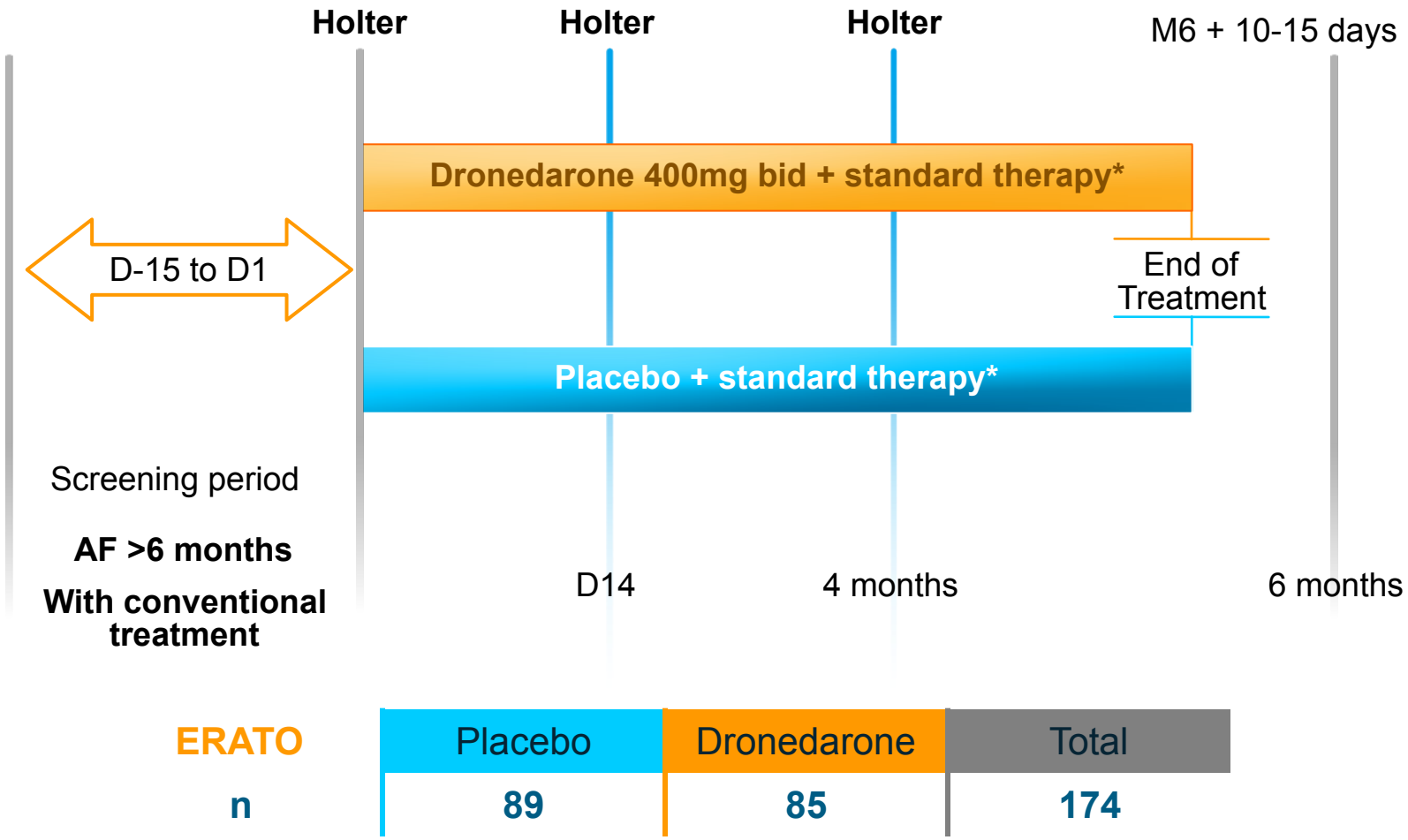
- Patients of had a history of unstable angina pectoris
- A history of torsades de pointes
- Baseline (D0) plasma potassium <3.5 mmol/L
- Third-degree atrioventricular block or significant sinus node disease
- New York Heart Association (NYHA) class III or IV congestive heart failure (CHF)
- Clinically relevant hematological, hepatic, gastrointestinal, renal, endocrinological, or psychiatric disease
- Patients taking other antiarrhythmic agents or any potent inhibitor of CYP3A4 were ineligible

* Symptomatic refers to any AF-related symptoms including palpitations

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

Study Design

Randomisation Dronedarone: placebo=1:1



ERATO	Placebo	Dronedarone	Total
n	89	85	174

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Baseline Patient Characteristics

Demographics	Placebo n=89	Dronedarone 400mg twice a day n=85
Male/Female (%)	62/27 (70/30)	58/27 (68/32)
White (%)	88 (99)	84 (99)
Mean age (range), (years)	66.4 (39-86)	65.2 (31-86)
Mean weight (range), (kg)	85.1 (54.0-133.2)	83.3 (48.0-122.0)

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

Baseline Cardiovascular Conditions

Cardiovascular history	Placebo n=89	Dronedarone 400mg twice a day n=85
Hypertension (%)	41 (46)	44 (52)
Structural heart disease (%)	34/85 (40)	31/82 (44)
Congestive heart failure (%)	32 (36)	37 (44)
NYHA class I (potential) (%)	8 (9)	12 (14)
NYHA class II (mild) (%)	24 (27)	25 (29)
Valvular heart disease including mitral valve prolapse (%)	16 (18)	14 (17)
Coronary heart disease (%)	14 (16)	16 (19)
Dilated cardiomyopathy (%)	10 (11)	8 (9)

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

Concomitant Medications

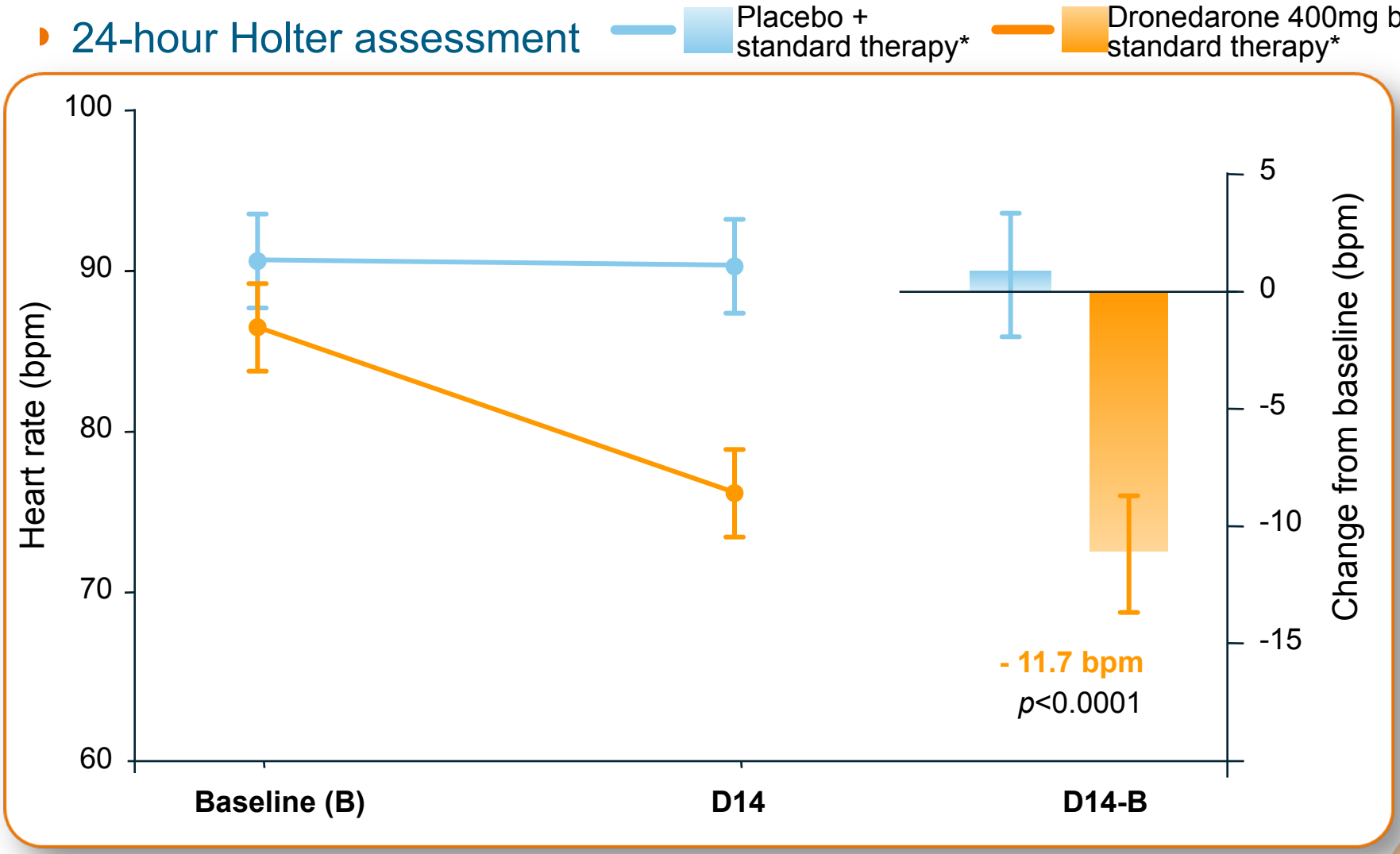
Concomitant medication use at D0	Placebo n=89	Dronedarone 400mg twice a day n=85
Oral anticoagulants (%)	80 (90)	73 (86)
Beta-blockers (except sotalol) (%)	44 (50)	46 (54)
ACEI or AIIRA (%)	43 (48)	43 (51)
ACEI (%)	35 (39)	32 (38)
AIIRA (%)	8 (9)	11 (13)
Diuretics (%)	34 (38)	43 (51)
Digoxin (%)	41 (46)	34 (40)
Calcium antagonists with HR lowering effects (%)	15 (17)	25 (29)
Statins (%)	20 (23)	19 (22)
Chronic antiplatelet therapy (%)	10 (11)	17 (20)
NSAIDS (%)	5 (6)	5 (6)

ACE-I=ACE inhibitor; AIIRA=Angiotensin II receptor antagonist; NSAID=non-steroid anti-inflammatory drug.

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

Dronedarone Significantly Decreased Ventricular Rate by 11.7 bpm

- 24-hour Holter assessment



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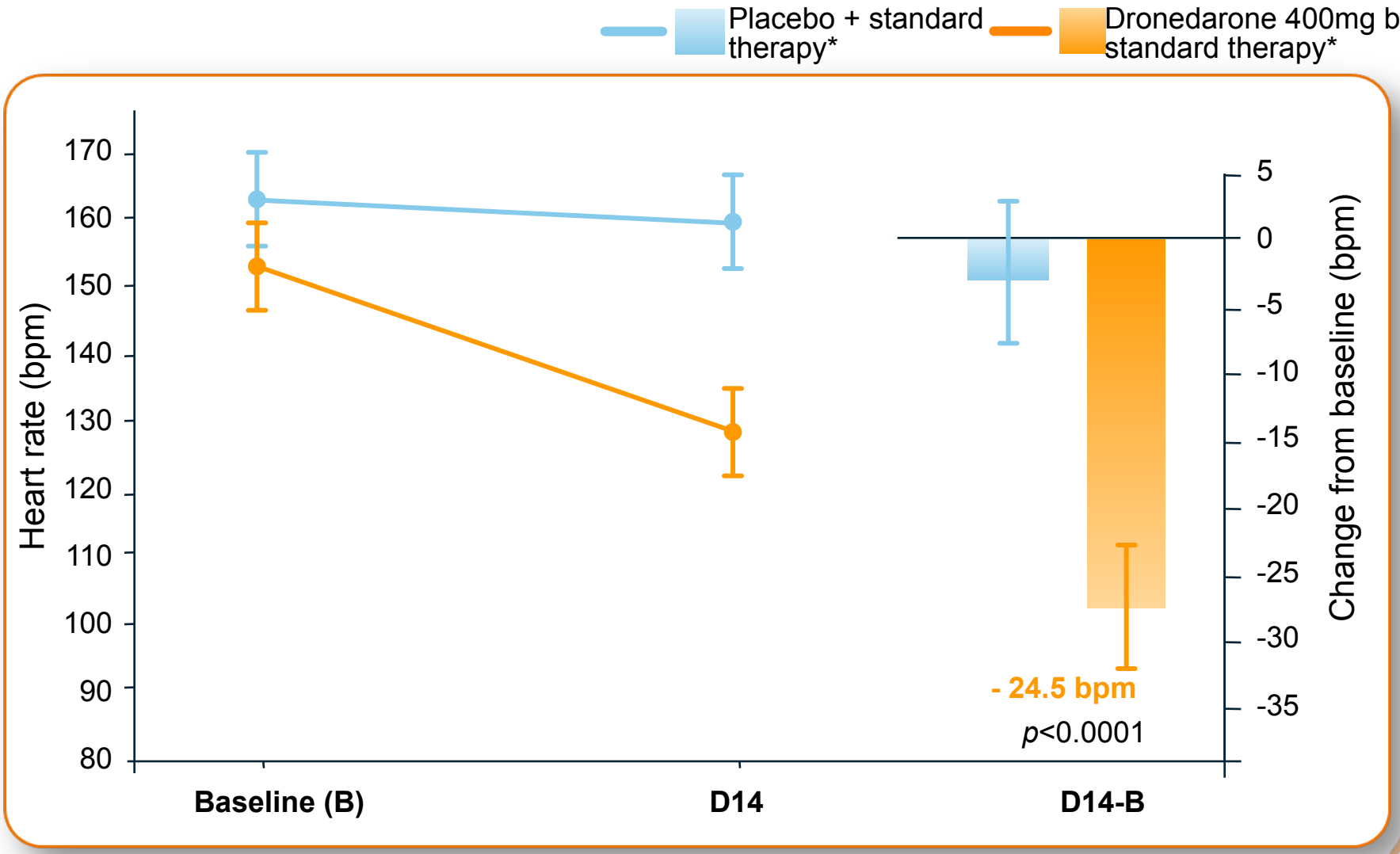
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

Dronedarone Significantly Decreased Maximal Exercise Ventricular Rate by 24.5bpm



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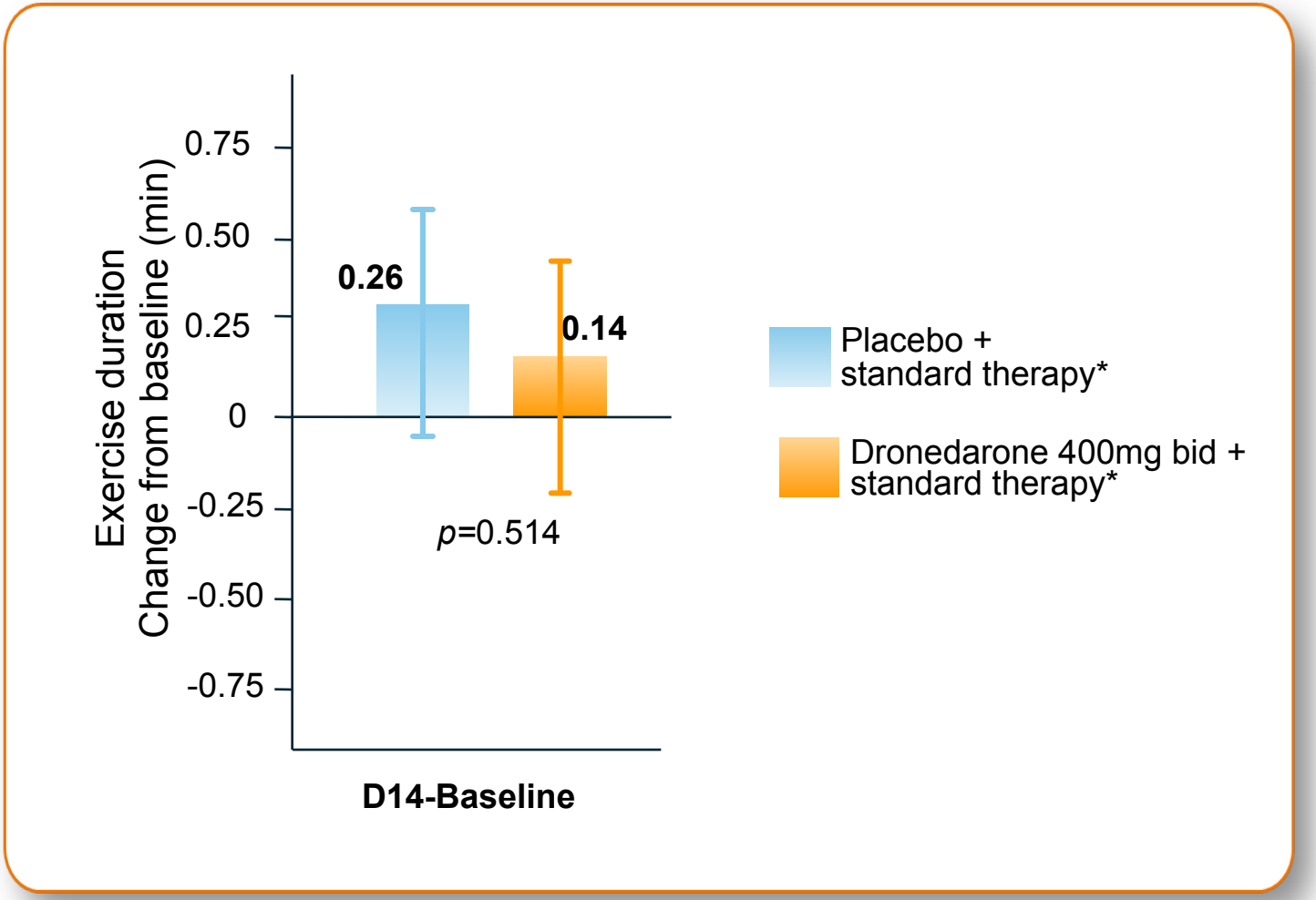
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

Dronedarone Controlled Rate Without Impairing Exercise Capacity



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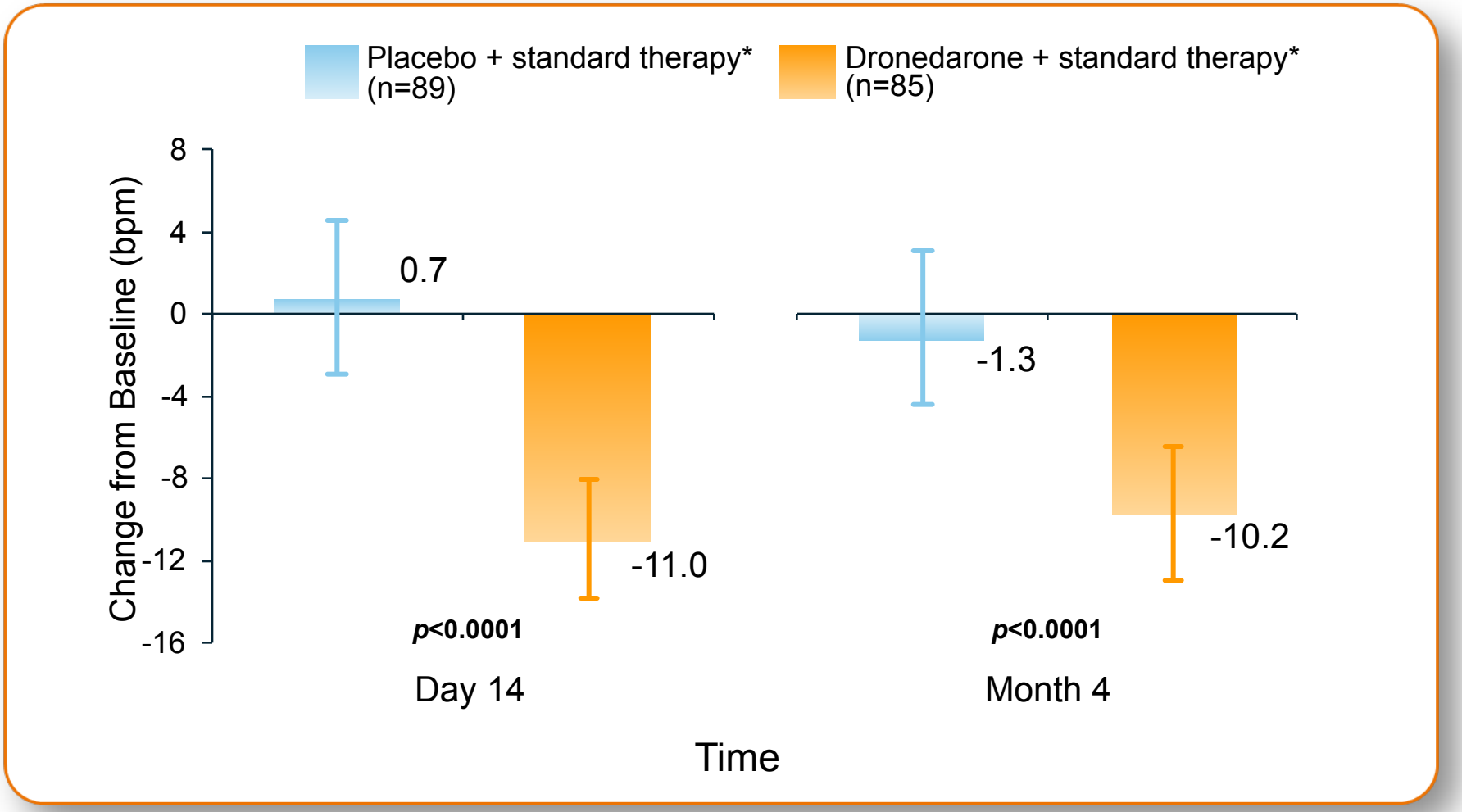
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

The Decrease in HR with Dronedarone was Sustained during Long-term Treatment



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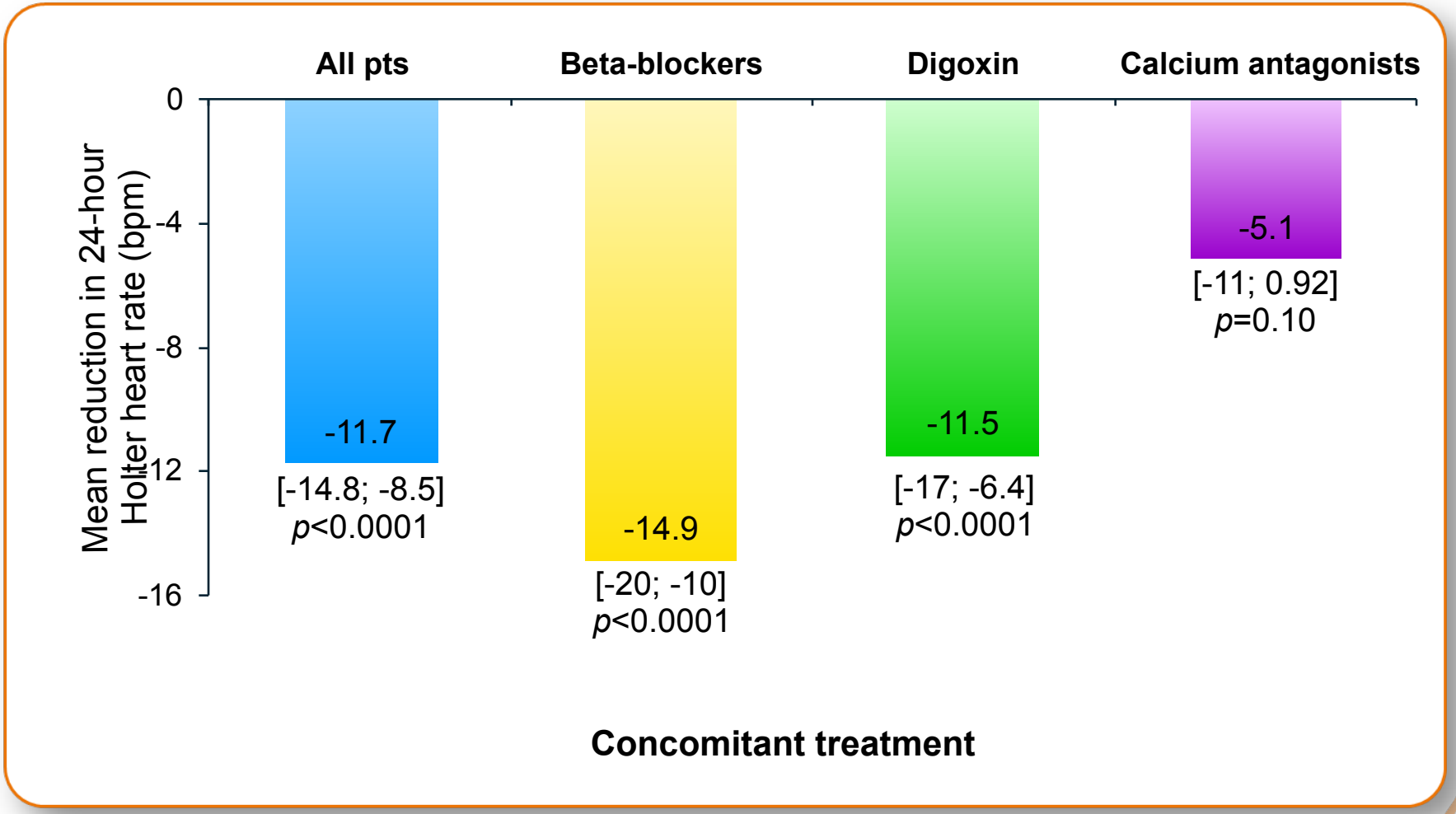
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

The Effects of Dronedarone were Additional to Other Rate-control Agents



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

Dronedarone Demonstrated a Favorable Safety Profile

Adverse Events	Placebo n=89 (%)	Dronedarone 400mg twice a day n=85 (%)
Any TEAE	53 (60)	65 (77)
Serious TEAEs	12 (14)	14 (17)
Deaths	0 (0)	1 (1)
Permanent discontinuations for any TEAEs	9 (10)	13 (15)

- No torsades de pointes reported

TEAE=Treatment-Emergent Adverse Event.
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

Conclusions

- ERATO was a pivotal study to confirm the benefit of dronedarone at providing incremental rate-control in patients with permanent AF treated with standard therapy
- ERATO demonstrated the clinically significant effect of dronedarone to consistently decrease heart-rate.
  The benefit was:
  - Above and beyond the effect of other rate-control agents
  - Sustained for 24-hours
  - Both at rest or during exercise
  - Achieved without impairing exercise capacity
- Dronedarone was well tolerated with no evidence of organ toxicity or proarrhythmias
- ERATO supports dronedarone's efficacy on rate-control and its safety in permanent patients

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

Clinical Trial Programme

Atrial Fibrillation

- 2a DAFNE
- 2b EURIDIS/ADONIS
- 2c ERATO
- 3a ATHENA

LV Dysfunction

- 2d ANDROMEDA

ANDROMEDA

ANtiarrhythmic trial with DRONaderone in Moderate to severe CHF Evaluating morbidity DecreAse

Objective

- ANDROMEDA was conducted in high-risk congestive heart failure (CHF) patients with left ventricular dysfunction and a recent acute decompensation and aimed to evaluate the potential benefit of dronedarone on all cause death or hospitalisation for worsening heart failure

- Patients were not selected based on AF / AFL history

- The populations enrolled in the ANDROMEDA and ATHENA studies were significantly different

Køber L, *et al. N Engl J Med.* 2008;358:2678-87; US Prescribing information

Study endpoints

- Primary endpoint
  - Death from any cause or hospitalisation for worsening heart failure
- Secondary endpoints
  - Death from all causes
  - Hospitalisation for cardiovascular causes
  - Hospitalisation for worsening heart failure
  - Occurrence of atrial fibrillation or flutter
  - Death from arrhythmia
  - Sudden death

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Inclusion and Exclusion Criteria

Inclusion criteria

- Consecutive hospitalised patients
- Age ≥18 years
- Presence of or suspected symptomatic CHF (current NYHA class II-IV) with
- At least one episode of decompensation corresponding to NYHA class III-IV within the last month
- Treated with a diuretic
- WMI ≤1.2 ~ LVEF ≤0.35
- Signed informed consent

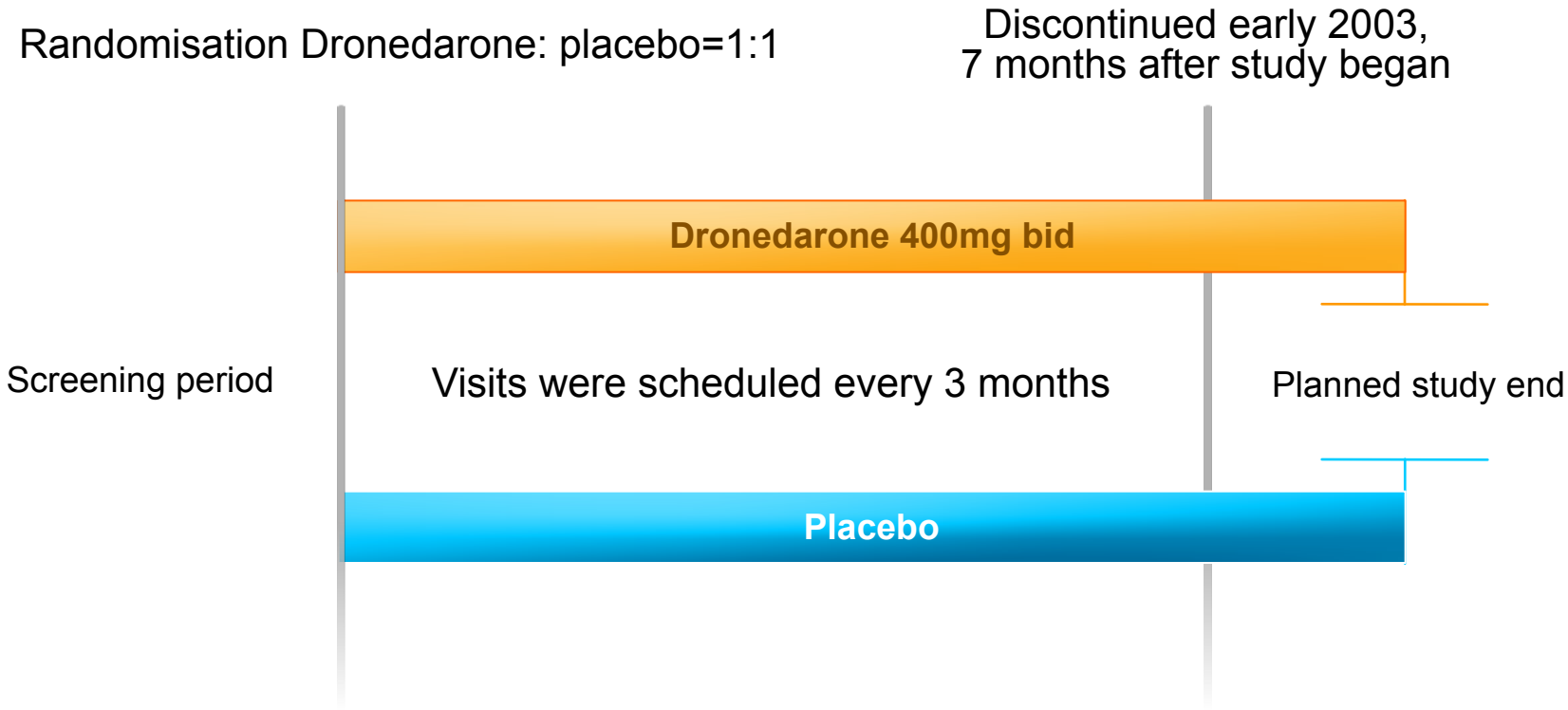
Exclusion criteria

- Acute myocardial infarction <7 days before screening
- Heart rate <50 beats per minute
- PR interval >0.28 second
- SA block or second or third-degree AV block not treated with a pacemaker
- History of torsades de pointes
- Corrected QT interval >500 msec
- Serum potassium <3.5 mmol per litre
- Use of class I or III antiarrhythmic drugs or drugs known to cause torsades de pointes
- Other serious disease including heart disease
- No restriction related to renal function

WMI: Wall-Motion Index

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Study Design



- Conducted at 72 hospitals in Denmark, Sweden, Norway, Poland, the Netherlands and Hungary
- A total of 627 patients (dronedarone, n=310 and placebo, n=317) of the 1000 planned had been enrolled

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Baseline Patient Characteristics: Patients were not selected based on history of AF/AFL

	Placebo n=317	Dronedarone 400mg bid n=310
Age (years) Median (range)	**72 (27-96)**	**71 (33-90)**
Weight (kg)	**79**	**78**
Gender [n (%)] Male	**242 (76.3%)**	**230 (74.2%)**
Wall motion index (WMI)		
Median (range)	**0.9 (0.3-1.2)**	**0.9 (0.3-1.2)**
NYHA class [n (%)]		
Class II	**121 (38.2%)**	**131 (42.3%)**
Class III	**183 (57.7%)**	**173 (55.8%)**
Class IV	**13 (4.1%)**	**6 (1.9%)**
Mean duration of heart failure (mo)	**23**	**20**
Estimated GFR (ml/min)		
Mean (range)	**52.8 (6-99)**	**50 (16-104)**
Atrial fibrillation or flutter mean (%)	**85 (26.8)**	**72 (23.2)**

WMI=Wall-Motion Index.

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

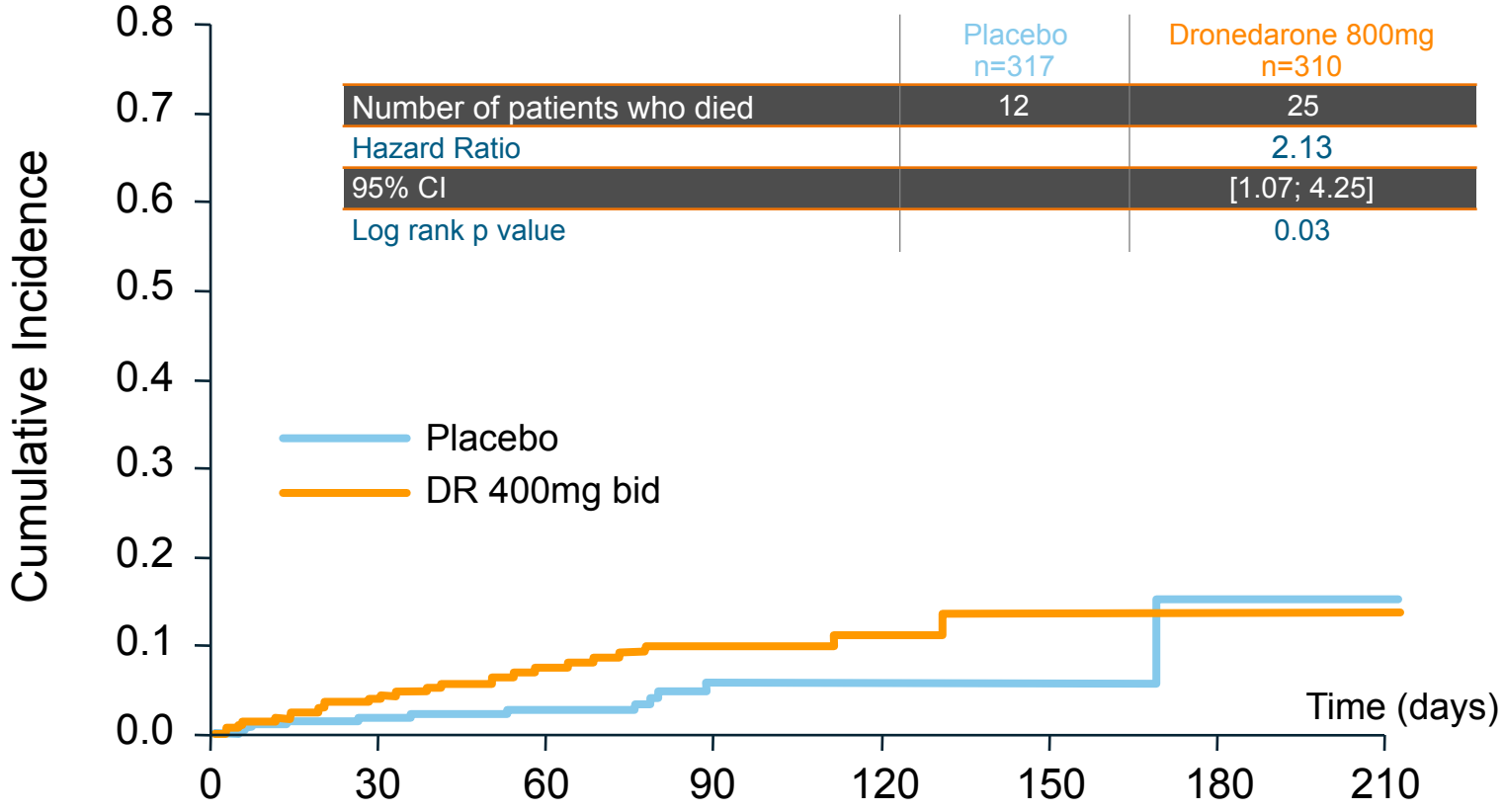
Concomitant Medications

	Placebo n=317 (%)	Dronedarone 400mg bid n=310 (%)
ACE inhibitor or ARB	267 (84.2)	274 (88.4)
Betablocker	192 (60.6)	192 (61.9)
Spironolactone	124 (39.1)	131 (42.3)
Diuretic (other than spironolactone)	302 (95.3)	288 (92.9)
Digitalis	101 (31.9)	96 (31.0)
Anticoagulant	102 (32.2)	92 (29.7)

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Cumulative Incidence of All-cause Mortality

	Placebo n=317	Dronedarone 800mg n=310
Number of patients who died	12	25
Hazard Ratio		2.13
95% CI		[1.07; 4.25]
Log rank p value		0.03

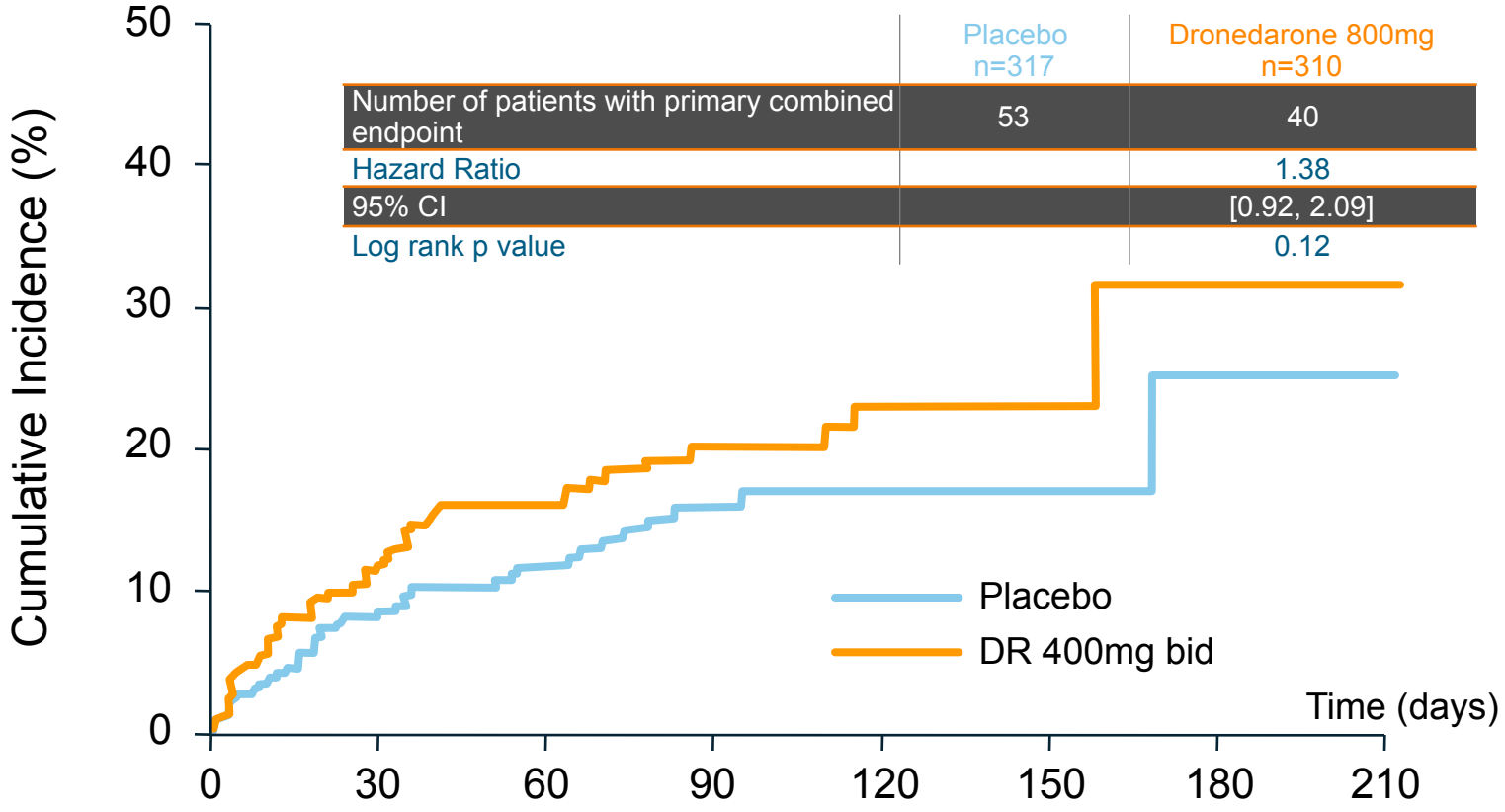


Patients at risk:

Placebo	317	256	181	103	50	18	6	1
DR 400mg bid	310	257	174	104	59	22	5	1

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

No Statistical Difference on The Primary Combined Endpoint of All-Cause Mortality or Hospitalisation for Worsening Heart Failure



Patients at risk:

Placebo	317	234	159	87	41	16	6	1
DR 400mg bid	310	232	151	87	49	19	4	1

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

No Significant Differences in SAEs Between Groups Except Creatinine Increase with Dronedarone

- Patients with serious adverse events (SAEs), excluding events resulting in death

Adverse Event	Placebo Group n=310	Dronedarone Group n=317
Any event	109 (34.4)	115 (37.1)
Any cardiac event	52 (16.4)	68 (21.9)
Cardiac failure	26 (8.2)	31 (10.0)
Angina pectoris	7 (2.2)	7 (2.3)
Myocardial infarction	4(1.3)	2 (0.6)
Ventricular fibrillation	3 (0.9)	1 (0.3)
Ventricular tachycardia	2 (0.6)	6 (1.9)
Noncardiac events		
Increase in serum creatinine	0 †	8 (2.6)
Any infection	9 (2.8)	9 (2.9)
Any gastrointestinal event	7 (2.2)	8 (2.6)
Any respiratory event	14 (4.4)	14 (4.5)
Surgical procedures		
Coronary-artery bypass	6 (1.9)	0
Coronary angioplasty	1 (0.3)	0
ICD placement	1 (0.3)	0

ICD=Imp
† p=0.01

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

ANDROMEDA Conclusions

- ANDROMEDA was conducted in a high risk CHF patients recently hospitalized for decompensation, most of whom did not have AF
- The populations enrolled in the ANDROMEDA and ATHENA studies were significantly different
- In these patients, dronedarone was not shown to be superior to placebo in decreasing mortality or CHF hospitalisations
- The excess of deaths were cardiac non-sudden deaths and were related to worsening heart failure
- No significant difference between placebo and dronedarone patients was seen for arrhythmic events and sudden deaths

Køber L, et al. N Engl J Med. 2008;358:2678-87. US Prescribing information

ANDROMEDA Conclusions

- No torsades de pointes reported, confirming the non-proarrhythmogenic profile of dronedarone, even in a highly susceptible population
- Since the study was stopped prematurely, no definitive conclusion can be drawn regarding safety of dronedarone in patients with unstable heart failure
  - However this negative outcome led to the exclusion of this hemodynamically unstable population in the following studies
- Following ANDROMEDA, ATHENA was conducted to establish the benefits of dronedarone in the targeted AF population and to confirm the good cardiac and extracardiac safety profile already observed in DAFNE, EURIDIS, ADONIS and ERATO, only excluding patients with unstable CHF

Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

Clinical Trial Programme

Atrial Fibrillation

- 2a DAFNE
- 2b EURIDIS/ADONIS
- 2c ERATO

LV Dysfunction

- 2d ANDROMEDA

- 3a ATHENA

ATHENA

A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter (AF/AFL)

ATHENA is a Unique Trial

- The largest single antiarrhythmic drug trial ever conducted in AF
  - >4,600 patients with a history of atrial fibrillation or atrial flutter
  - More than 550 investigational sites in 37 countries
- Patients enrolled in ATHENA were representative of the general AF population
- Unique endpoints for an AF trial
  - Combined endpoint of cardiovascular hospitalisation or death
  - First AF trial to use "non-conventional" endpoints

Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Before ATHENA, AF Trials Adopted an "ECG focused" Approach

Rhythm Control

- Time to first recurrence of AF
- Percentage of patients remaining in sinus rhythm at a given point of time

Identified by:

- Routine ECGs/symptomatic ECGs
- Prolonged monitoring: event recorders, automated recorders

Rate Control

- Ventricular rate in AF
  - ECG, Holter, graded exercise test (GXT)

Camm AJ, *et al. EHJ* 2008;10 (suppl. H) H55-H78.

For the First Time in AF, ATHENA Adopted an "Outcomes Focused" Approach

- Morbid events:
  - Hospitalisation
  - Hospitalisation for cardiovascular events
- Death
  - All cause death
  - Cardiovascular death

- ATHENA examined unique outcomes endpoints for an AF clinical trial

Kirchhof P, *et al. Europace* 2007;9:1006-1023.

Objective

- Evaluate the efficacy and safety of dronedarone 400mg bid vs placebo on top of standard therapy* in the prevention of CV hospitalisation or death from any cause over a minimum treatment and follow-up duration of 12 months in patients with paroxysmal or persistent AF/AFL

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Study Endpoints

- Primary endpoint
  - Combined endpoint of cardiovascular hospitalisation and death from any cause
- Secondary endpoints
  - Death from any cause
  - Cardiovascular death
  - Hospitalisation for cardiovascular reasons
- Safety endpoint
  - Incidence of treatment emergent adverse events including all adverse events, serious adverse events, and adverse events leading to study drug discontinuation

Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Inclusion and Exclusion Criteria

Inclusion criteria

- High-risk patients with a history of paroxysmal or persistent AF/AFL
- Aged ≥75 years with or without additional risk factors
- Aged ≥70 years and ≥1 risk factor (hypertension; diabetes; prior stroke/ TIA; LA ≥50 mm; LVEF <0.40)

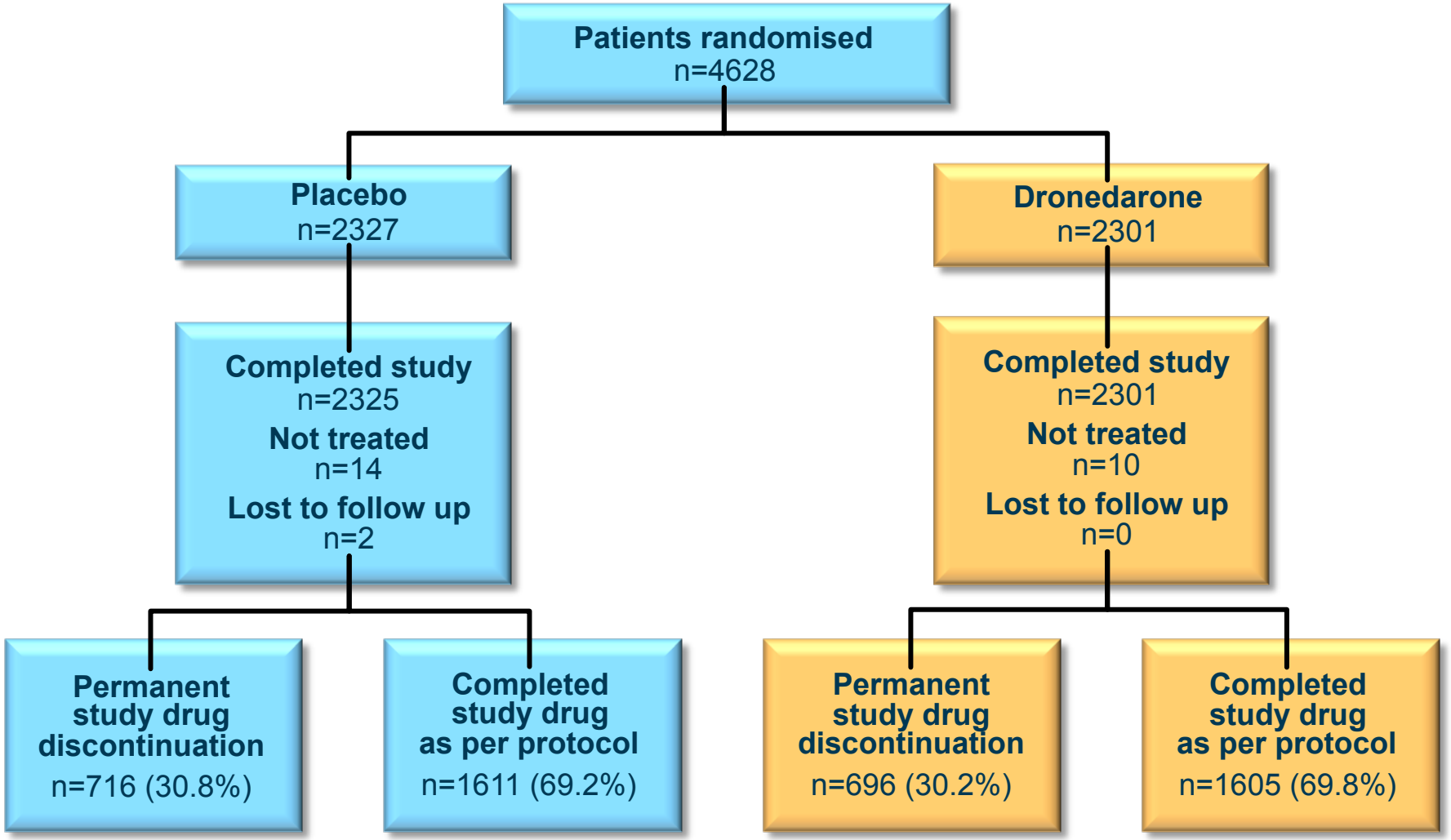
- **Originally the protocol had allowed patients <70 years of age with additional risk factors into the study**
- **The protocol was subsequently amended to include only patients ≥70 years of age**

Exclusion criteria

- Permanent AF
- Unstable hemodynamic situation (i.e. recently decompensated CHF)
- CHF NYHA class IV
- Bradycardia <50 bpm and/or PR >0.28 sec
- Sick sinus syndrome
- Calculated GFR at baseline <10 ml/min
- Potassium <3.5 mmol/L
- Concomitant antiarrhythmic drug Rx
- Severe illness limiting life expectancy
- Pregnancy or breastfeeding
- Refusal or inability to give informed consent

Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Study Flow



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

Baseline Patient Characteristics

	Placebo n=2327	Dronedarone n=2301	All patients n=4628
Age (mean ±SD, years)	71.7 ±9.0	71.6 ±8.9	72 ±9.0
<65yr	442 (19.0%)	431 (18.7%)	873 (18.9%)
65 to 75yr	907 (39.0%)	923 (40.1%)	1830 (39.5%)
≥75yr	978 (42.0%)	947 (41.2%)	1925 (41.6%)
Female gender	1038 (44.6%)	1131 (49.2%)	2169 (46.9%)
AF/AFL at baseline	586 (25.2%)	569 (24.7%)	1155 (25.0%)
Structural heart disease	1402 (60.9%)	1330 (58.3%)	2732 (59.6%)
Hypertension	1996 (85.8%)	1999 (86.9%)	3995 (86.3%)
Coronary heart disease	737 (31.7%)	668 (29.0%)	1405 (30.4%)
Valvular heart disease	380 (16.3%)	379 (16.5%)	759 (16.4%)
Non-ischemic cardiomyopathy	131 (5.6%)	123 (5.3%)	254 (5.5%)
History of CHF NYHA II/III	515 (22.1%)	464 (20.2%)	979 (21.2%)
LVEF <0.45	285/2281 (12.5%)	255/2263 (11.3%)	540/4544 (11.9%)
LVEF <0.35	87/2281 (3.8%)	92/2263 (4.1%)	179/4544 (3.9%)
Lone atrial fibrillation	139 (6.0%)	140 (6.1%)	279 (6.0%)
Pacemaker	243 (10.4%)	214 (9.3%)	457 (9.9%)

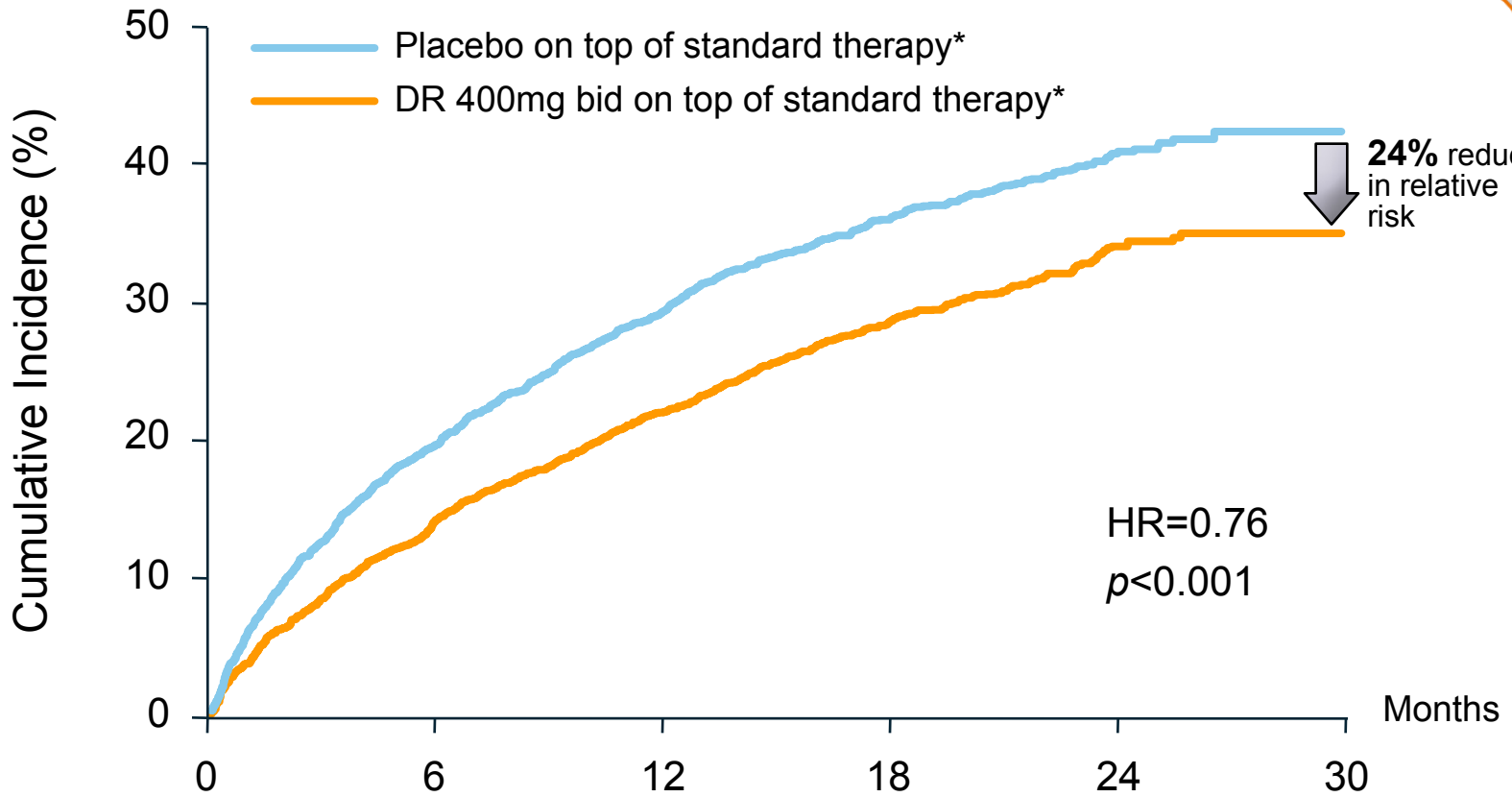
Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Concomitant Medications

		Placebo n=2327	Dronedarone n=2301	All patients n=4628
Rate Control Agents	Betablocker	1641 (70.5%)	1628 (70.8%)	3269 (70.6%)
	Ca-antagonists	307 (13.2%)	331 (14.4%)	638 (13.8%)
	Digoxin	308 (13.2%)	321 (14.0%)	629 (13.6%)
	ACE/ARB	1602 (68.8%)	1614 (70.1%)	3216 (69.5%)
	Statins	914 (39.2%)	878 (38.2%)	1792 (38.7%)
Anti-thrombotics	Vit. K antagonists	1384 (59.5%)	1403 (61.0%)	2787 (60.2%)
	Aspirin	1019 (43.8%)	1018 (44.2%)	2037 (44.0%)

Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Dronedarone Significantly Decreased Risk of CV Hospitalisation or Death by 24%



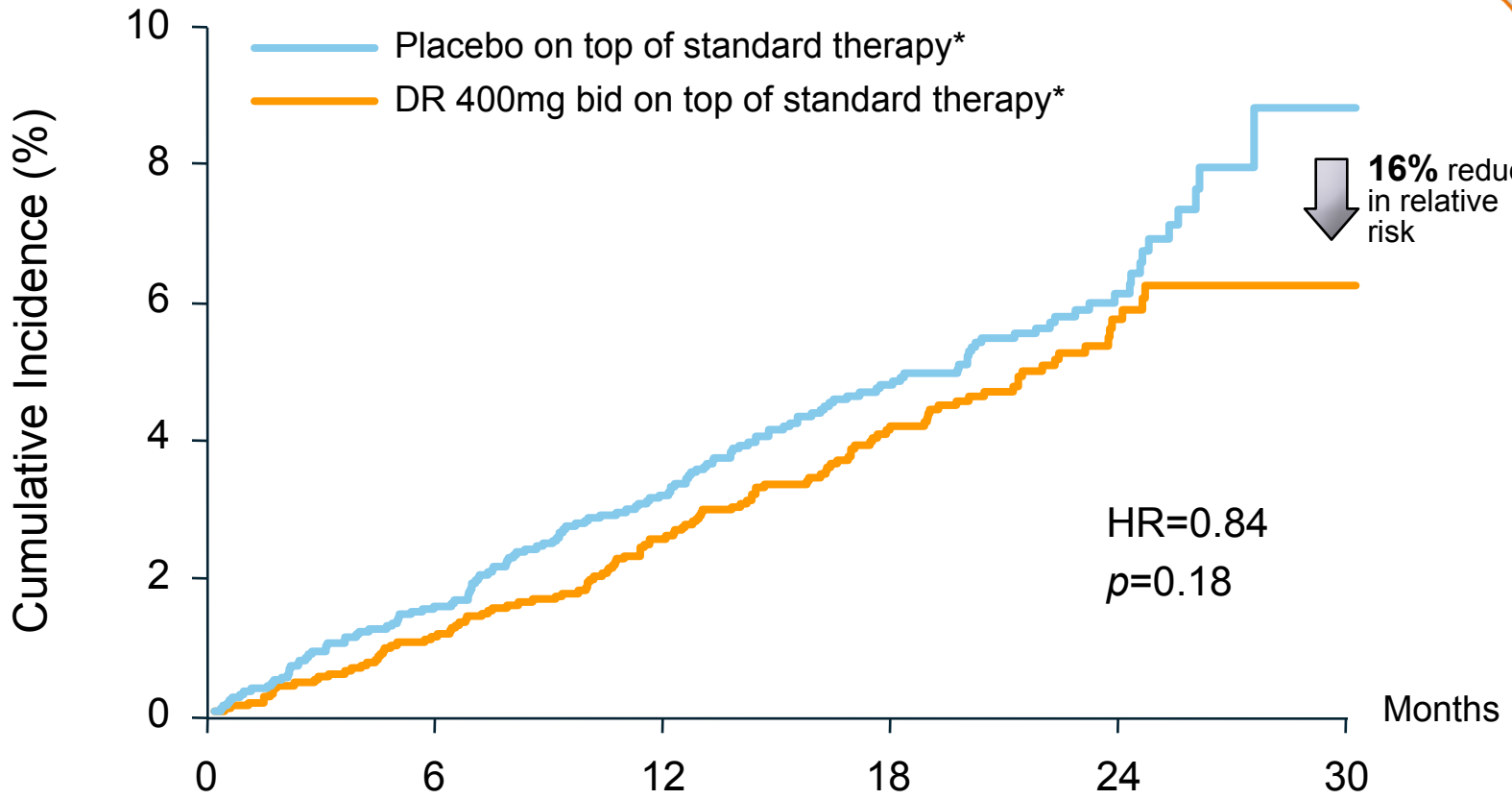
Patients at risk:

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

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

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

Dronedarone Reduced Risk of All-cause Death by 16%



Patients at risk:

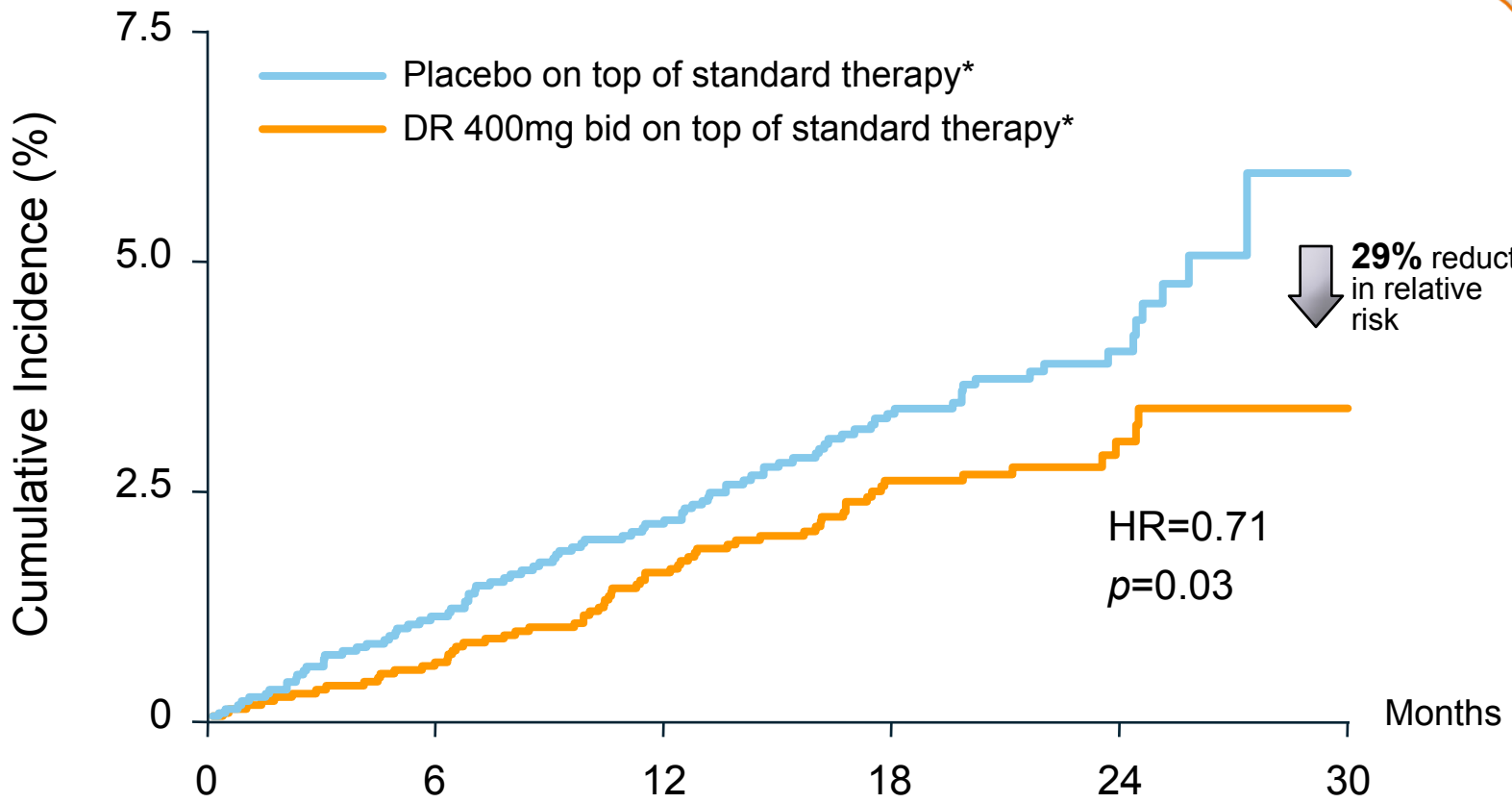
Placebo	2327	2290	2250	1629	636	7
DR 400mg bid	2301	2274	2240	1593	615	4

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

Mean follow-up 21 ±5 months.

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

Dronedarone Significantly Decreased Risk of Cardiovascular Death by 29%



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Mean follow-up 21 ±5 months.

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

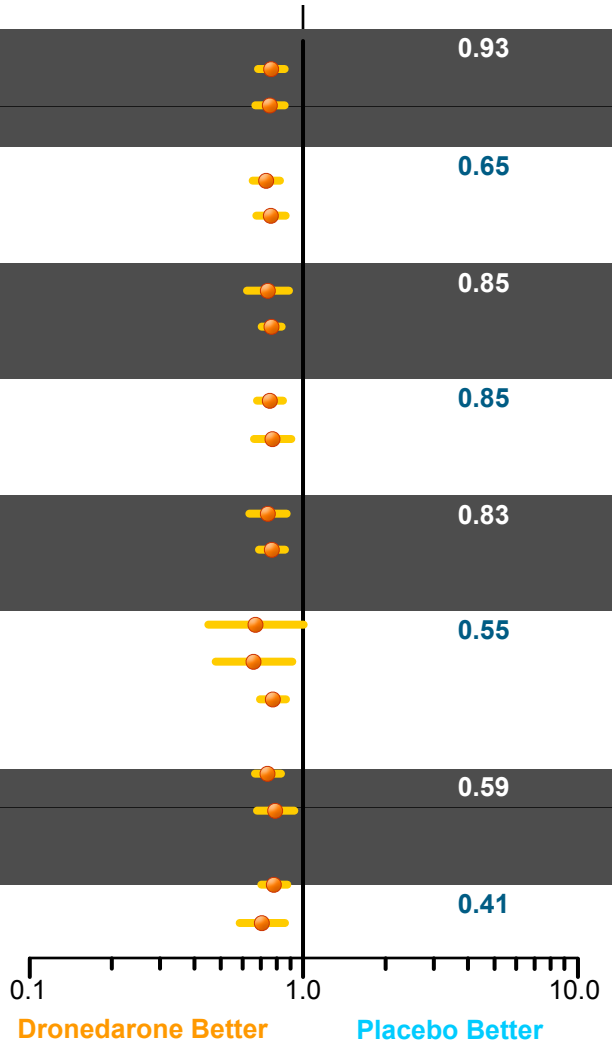
Dronedarone Significantly Decreased Risk of Arrhythmic Death by 45% and CV death by 29%

	Placebo n=2327	Dronedarone n=2301	HR	95% CI	*p 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**

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

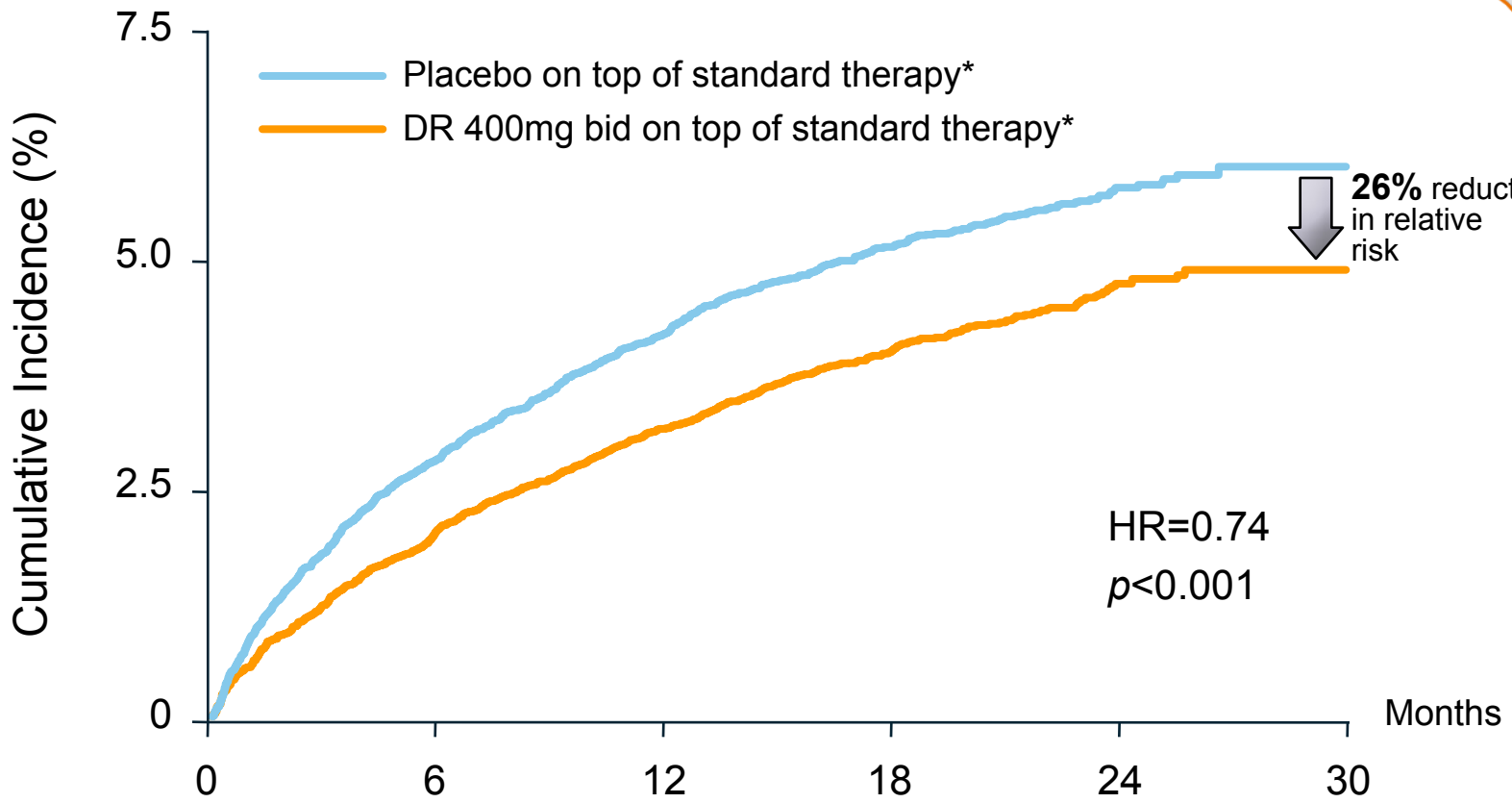
Dronedarone Reduced CV Hospitalisation or All-cause Death Across Important Subgroups

Characteristic	n	HR (95% CI)	*p* value for interaction
Age (years)			**0.93**
<75	**2703**	**0.76 (0.67–0.87)**	
≥75	**1925**	**0.75 (0.65–0.87)**	
Gender			**0.65**
Male	**2459**	**0.74 (0.64–0.85)**	
Female	**2169**	**0.77 (0.67–0.89)**	
Presence of AF/AFL			**0.85**
Yes	**1155**	**0.74 (0.61–0.91)**	
No	**3473**	**0.76 (0.68–0.85)**	
Structural Heart Disease			**0.85**
Yes	**2732**	**0.76 (0.67–0.85)**	
No	**1853**	**0.77 (0.65–0.92)**	
Congestive Heart Failure			**0.83**
Yes	**1365**	**0.75 (0.64–0.88)**	
No	**3263**	**0.76 (0.68–0.86)**	
LVEF (%)			**0.55**
<35	**179**	**0.68 (0.44–1.03)**	
[35-45[	**361**	**0.66 (0.47–0.92)**	
≥45	**4004**	**0.78 (0.70–0.86)**	
ACE/ARB			**0.59**
Yes	**3216**	**0.74 (0.66–0.83)**	
No	**1412**	**0.79 (0.66–0.95)**	
Beta Blocking Agents			**0.41**
Yes	**3269**	**0.78 (0.69–0.87)**	
No	**1359**	**0.71 (0.58–0.86)**	



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

Dronedarone Significantly Decreased Cardiovascular Hospitalisation by 26%



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

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other cardiovascular therapy such as ACE inhibitors and statins.

Dronedarone Significantly Decreased Hospitalisations Related to AF by 37%

Reason for first CV hospitalisation	Placebo n=2327	Dronedarone n=2301	HR	95% CI	*p* value
Any reason	**859**	**675**	**0.74**	**0.67; 0.82**	**<0.001**
Atrial Fibrillation	**510**	**335**	**0.63**	**0.55; 0.72**	**<0.001**
CHF	**132**	**112**	**0.86**	**0.67; 1.10**	**0.22**
ACS	**89**	**62**	**0.70**	**0.51; 0.97**	**0.03**
Syncope	**32**	**27**	**0.85**	**0.51; 1.42**	**0.54**
Ventricular arrhythmia or cardiac arrest	**12**	**13**	**1.09**	**0.50; 2.39**	**0.83**

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

Adverse Event Rates were Not Significantly Different Between Dronedarone and Placebo Groups

Randomised and treated patients	Placebo n=2313	Dronedarone n=2291	*p* value
Patients with any TEAE	**1603 (69.3%)**	**1649 (72.0%)**	**0.048**
Cardiac events	**221 (9.6%)**	**260 (11.3%)**	**0.048**
Bradycardia	**28 (1.2%)**	**81 (3.5%)**	**<0.001**
QT-interval prolongation	**14 (0.6%)**	**40 (1.7%)**	**<0.001**
Gastrointestinal	**508 (22.0%)**	**600 (26.2%)**	**<0.001**
Respiratory	**337 (14.6%)**	**332 (14.5%)**	**0.97**
Skin	**176 (7.6%)**	**237 (10.3%)**	**0.001**
Creatinine increase	**31 (1.3%)**	**108 (4.7%)**	**<0.001**
Patients with any serious TEAE	**489 (21.1%)**	**456 (19.9%)**	**0.31**
Cardiac events	**15 (0.6%)**	**15 (0.7%)**	**1.00**
Respiratory	**45 (1.9%)**	**41 (1.8%)**	**0.74**
Gastrointestinal	**68 (2.9%)**	**81 (3.5%)**	**0.28**
Creatinine increase	**1 (<0.1%)**	**5 (0.2%)**	**0.12**
Skin	**6 (0.3%)**	**7 (0.3%)**	**0.79**
Patients permanently discontinued study drug for any TEAE	**187 (8.1%)**	**290 (12.7%)**	**<0.001**

TEAE=Treatment Emergent Adverse Events.
Adapted from Hohnloser SH *et al. N Engl J Med 2009;360:668-78.*

Conclusions

- The landmark ATHENA trial is the largest morbidity-mortality study with an AAD ever conducted in AF patients
- Dronedarone is the only AAD ever to demonstrate a significant reduction in CV hospitalisation or death
- The reduction in CV hospitalisation or death was consistent across all subgroups in a population representative of the AF population
- Dronedarone also significantly reduced cardiovascular mortality, specifically arrhythmic death
- Dronedarone significantly reduced the incidence of CV hospitalisations
  - For AF-related as well as non-AF-related reasons
- The unique CV outcomes observed in ATHENA with dronedarone were achieved without serious safety concerns with a low risk for pro-arrhythmia and no organ toxicity

Dronedarone Conclusions

Overall Conclusions

- Atrial Fibrillation is the most common cardiac arrhythmia and increases patients' risk of stroke, heart failure and death, including sudden cardiac death, thereby contributing to an increased risk of CV morbidity and mortality
- Dronedarone is the only anti-arrhythmic drug ever proven to have significantly reduced CV hospitalisation or mortality, in ATHENA, the largest AAD trial in atrial fibrillation
- Dronedarone exhibits both rhythm and rate control properties and has been proven to significantly prolong time to AF recurrence and decrease ventricular rate
- Dronedarone demonstrates a low risk of pro-arrhythmia, cardiac and extra-cardiac toxicity, with favourable tolerability
    - However, ANDROMEDA results preclude its use in patients with unstable heart failure, such as patients with Class IV heart failure or recent hospitalization for decompensation of heart failure
- Dronedarone is easy-to-use because of its fixed-dosing regimen, outpatient initiation and minimal monitoring requirements
- Dronedarone is the only anti-arrhythmic drug proven to reduce CV hospitalisation or mortality in AF patients, excluding those with unstable heart failure, whilst also prolonging time to AF recurrence and providing rate control - all achieved with a favourable safety profile

DRONEDARONE

A New Anti-Arrhythmic Drug
for the Treatment of Atrial Fibrillation/Atrial Flutter

Dronedarone is approved by the FDA and under EMEA review. All information is provided for scientific purpose exclusively.

GLM.DRO.09.07.14