Antiarrhythmics for atrial fibrillation – focus on dronedarone

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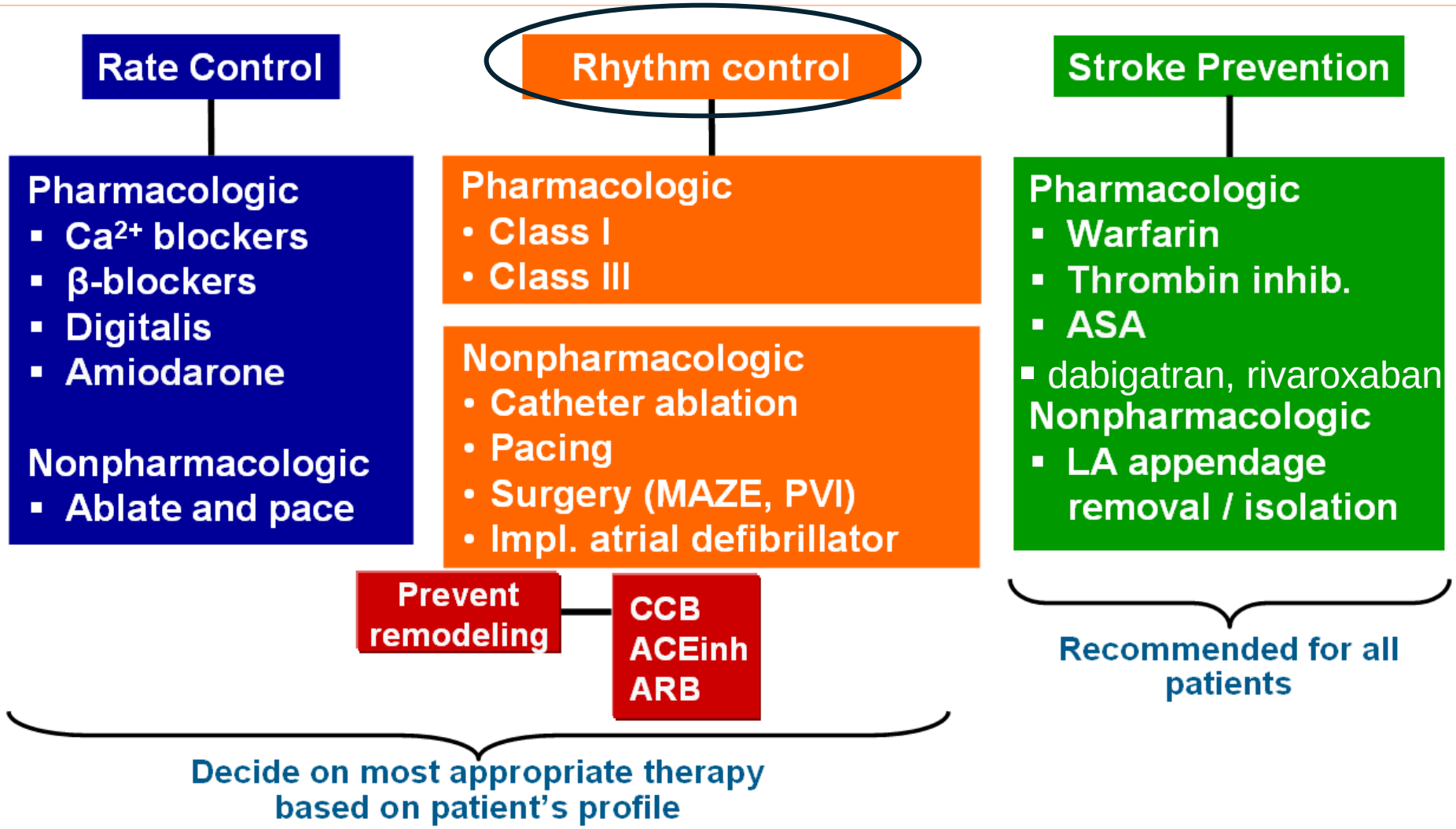
AF facts

- Progressive disease
- Increases risk of death ~2-fold
- Increases risk of stroke ~5-fold
- Longer time in AF => progression to permanent AF
- Synus rhythm is „God given”

What can we do to minimize ”bad” and maximize „good” facts?



Adapted from Prystowsky EN. *Am J Cardiol*. 2000;85:3D-11D. Modified by J Reiffel.
Fuster V, et al. *Circulation*. 2006;114:e257-e354.

Chronology antiarrhythmics

1785 Digitalis

1918 Quinidine

1936 Procainamide

1948 Lidocaine

1950 Phenytoin

1954 Disopyramide

1958 Ajmaline

1962 β-blocker

1964 Propafenon

1982 Flecainide

1982 Amiodarone

1994 Adenosine

1995 Ibutilide

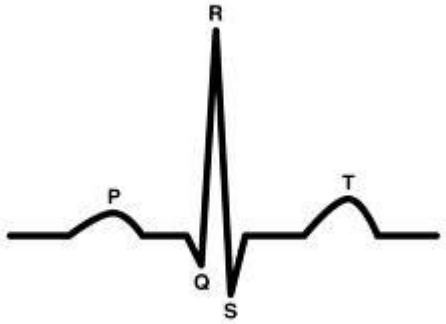
1999 Dofetilide

2009 Dronedarone

2010 Vernakalant

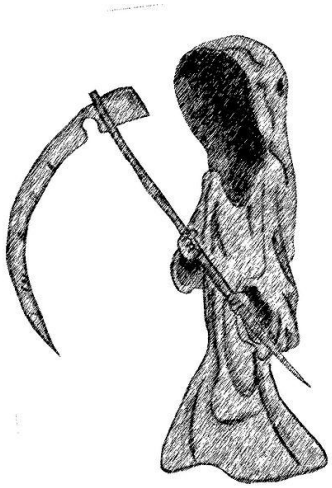
The purpose of antiarrhythmics

- EKG: SR, prevent Afib; SVT; VA



- symptoms, hospitalization

- mortality



The dissapointment

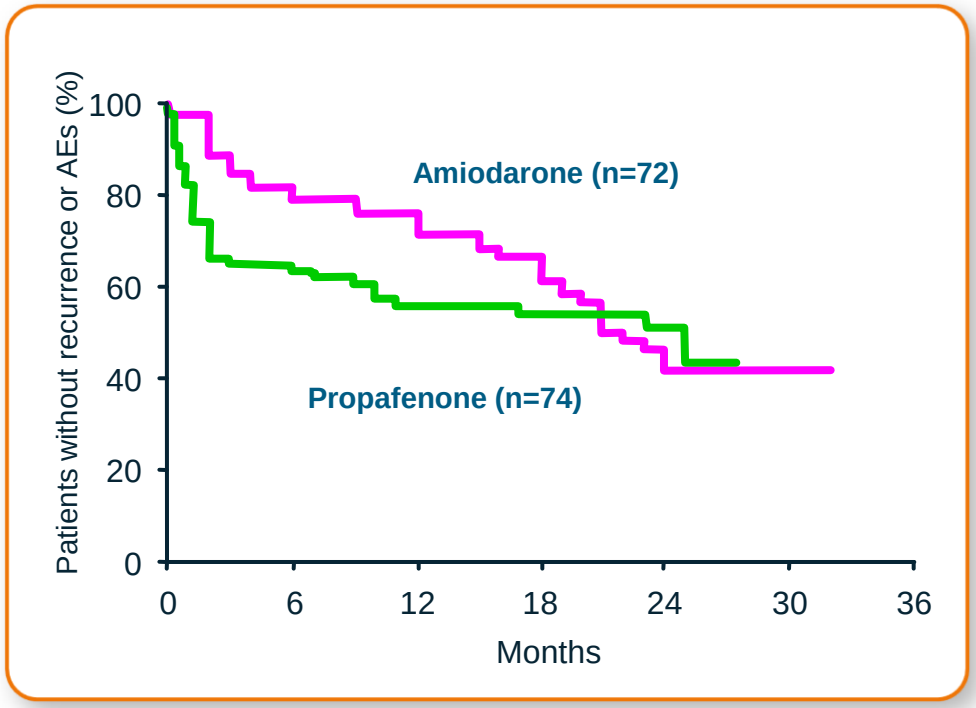
- Interventions with superior effect on mortality are treating the consequences of arrhythmia:
  - anticoagulation
  - ICDs

Side effects

I stopped taking the medicine because I prefer the original disease to the side effects

Amiodarone - effect of reducing AF recurrence fades in the long term

Primary analysis



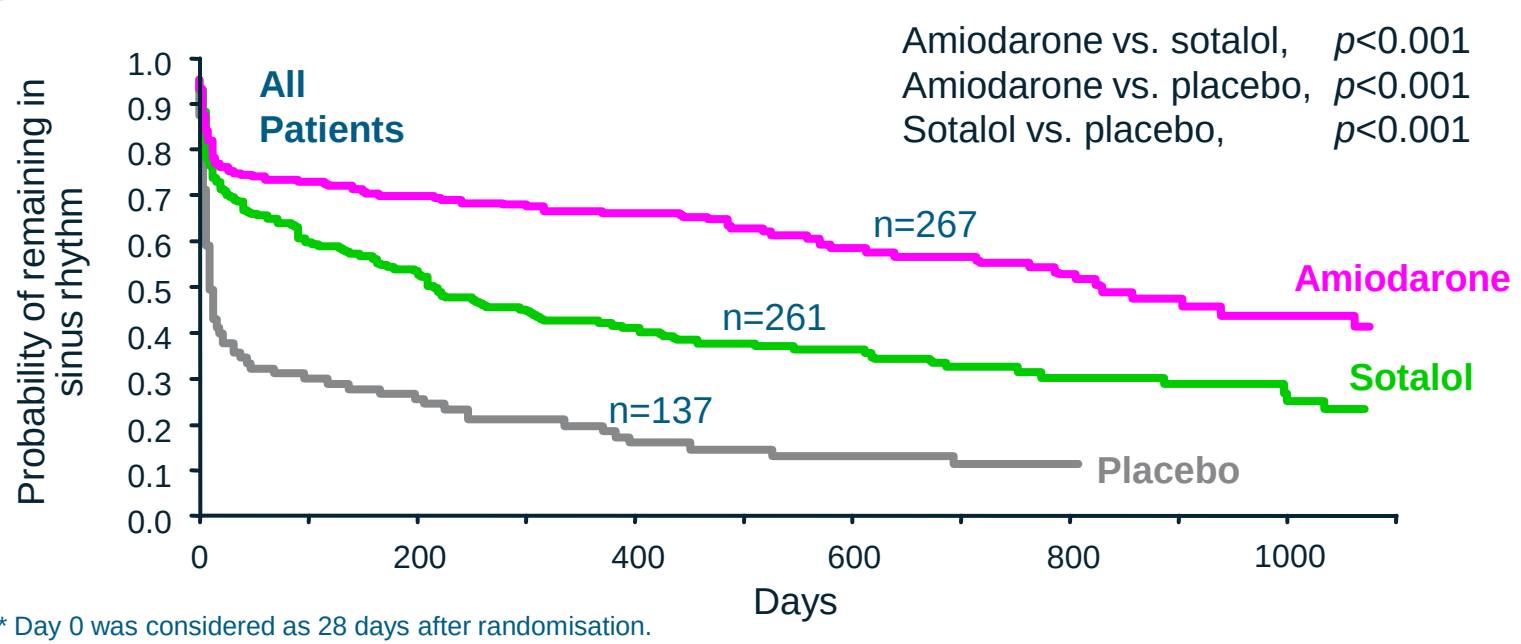
- **A comparative study of low dose amiodarone and low dose propafenone after restoration of sinus rhythm showed that the efficacy of amiodarone is offset by a higher discontinuation rate due to AEs in the long term:**
  - 17% of patients receiving low dose amiodarone vs 3% receiving low dose propafenone (within 2 years)

Adapted from Kochiadakis GE, *et al. Chest.* 2004;125;377-83.

AEs: adverse events

Despite better maintenance of SR with amiodarone vs. sotalol, there was a trend towards increased mortality vs. placebo

SAFE-T study: Primary endpoint



* Day 0 was considered as 28 days after randomisation.

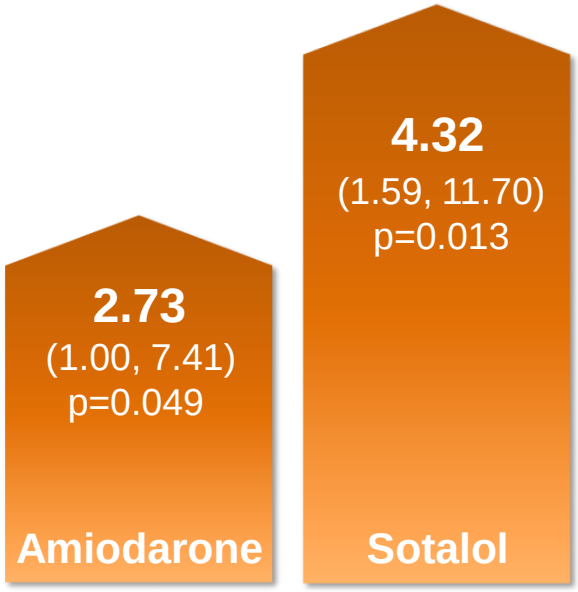
	Deaths (N)	Mortality ratio adjusted for duration of follow-up	P value vs. placebo
Amiodarone	13	1.3	*p*=0.19
Sotalol	15	1.8	*p*=0.11
Placebo	3	1	

Adapted from Singh BN, *et al. N Eng J Med* 2005;352:1861–72.

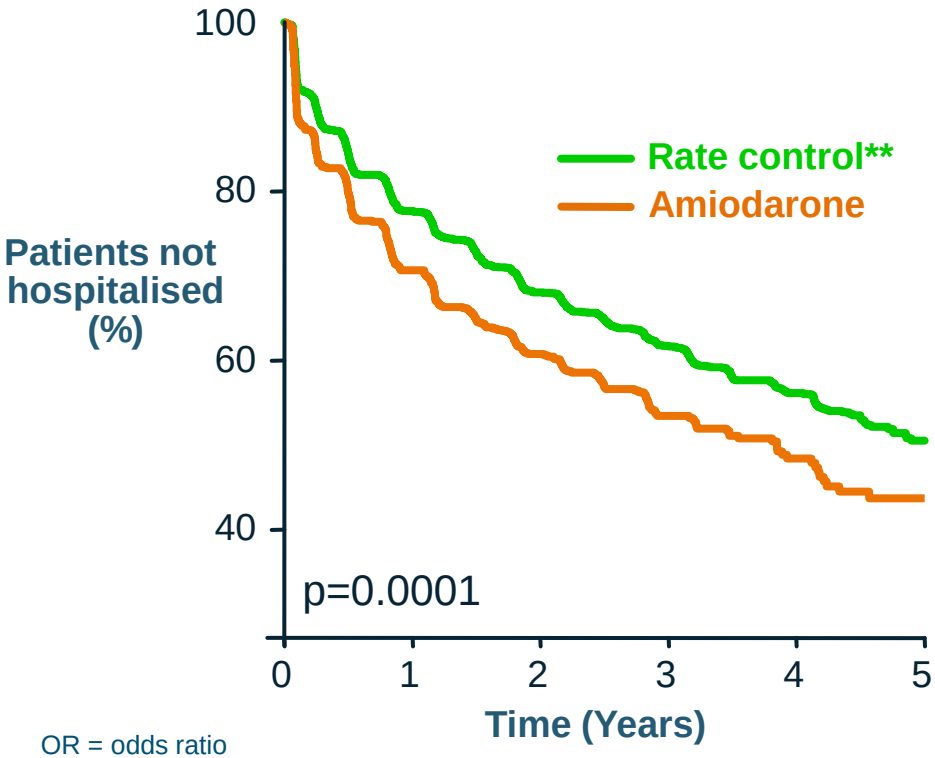
Older AADs may increase the risk of mortality and CV hospitalisation

Risk of mortality*[1]

OR (95% CI) vs. placebo



CV hospitalisation[2]



* Mixed treatment comparison of seven large scale clinical trials OR = odds ratio

** Rate control may include digoxin, metoprolol, atenolol, propranolol, diltiazem, and verapamil

Adapted from:

1. Freemantle N, *et al*. Europace 2011; 13: 329–45
2. Slee A, *et al.* Circulation 2009; 120: S692

Dronedarone ?

The most extensively studied AAD in AF; > 10,000 patients phase 2/3 clinical trials programme

Studies	N	Population	Objectives
Rhythm and Rate Control			
DAFNE	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS	612	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ADONIS	625	Paroxysmal/Persistent AF/AFL	Maintenance of sinus rhythm
ERATO	174	Permanent AF	Ventricular rate control
DIONYSOS	504	Persistent AF	Comparative trial vs amiodarone
Recently Decompensated CHF			
ANDROMEDA	627 / 1000	Unstable CHF and LV dysfunction (25% AF)	Morbidity-mortality study
Clinical Outcomes			
ATHENA	4628	Paroxysmal/Persistent AF/AFL	Prevention of cardiovascular hospitalisation or death from any cause
PALLAS	3149 / 10800	Permanent AF	Prevention of major CV events and CV hospitalisation or death from any cause

For the first time in AF, ATHENA adopted an "outcomes focused" approach

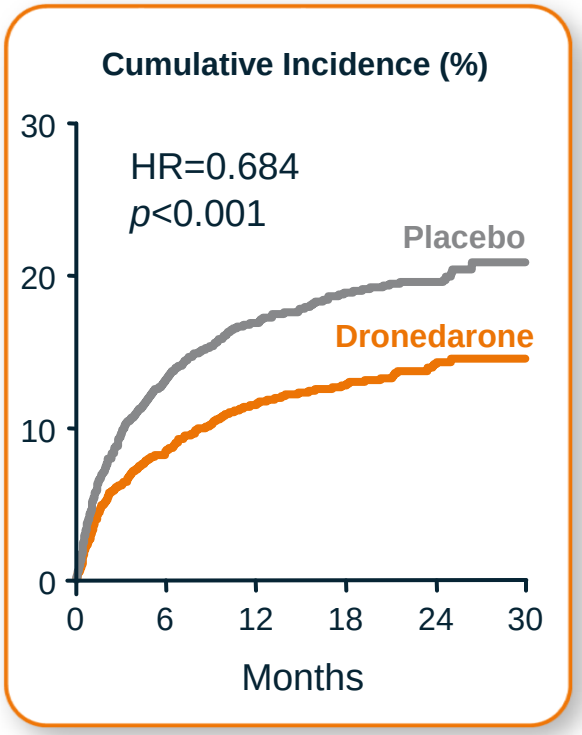
- The largest single antiarrhythmic drug trial ever conducted in AF
  - >4,600 patients with a history of atrial fibrillation or atrial flutter
  - More than 550 investigational sites in 37 countries
- ATHENA's objective:
  - Evaluate the efficacy and safety of dronedarone vs. placebo on top of standard therapy* in the **prevention of CV hospitalisation or death from any cause** in patients with paroxysmal or persistent AF/AFL

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and /or aspirin and other antiplatelets therapy) and/or other CV agents such as ACEIs/ARBs and statins

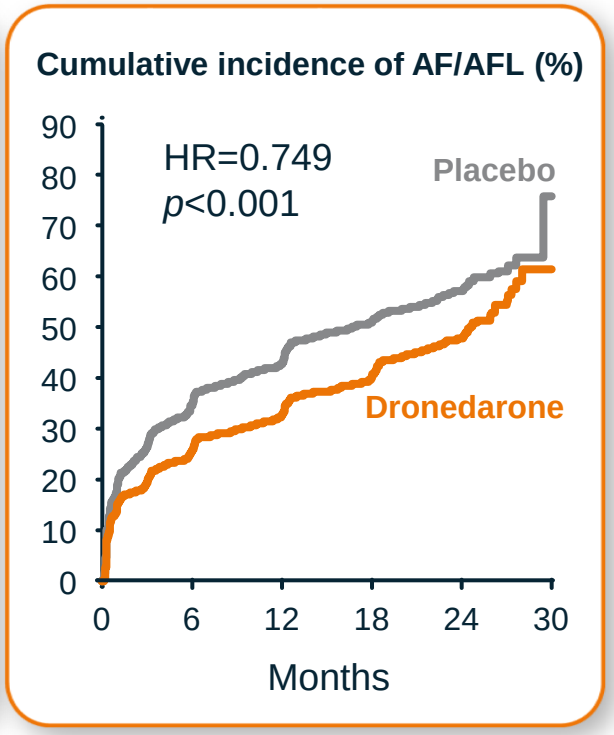
Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Was dronedarone an effective AAD in ATHENA?

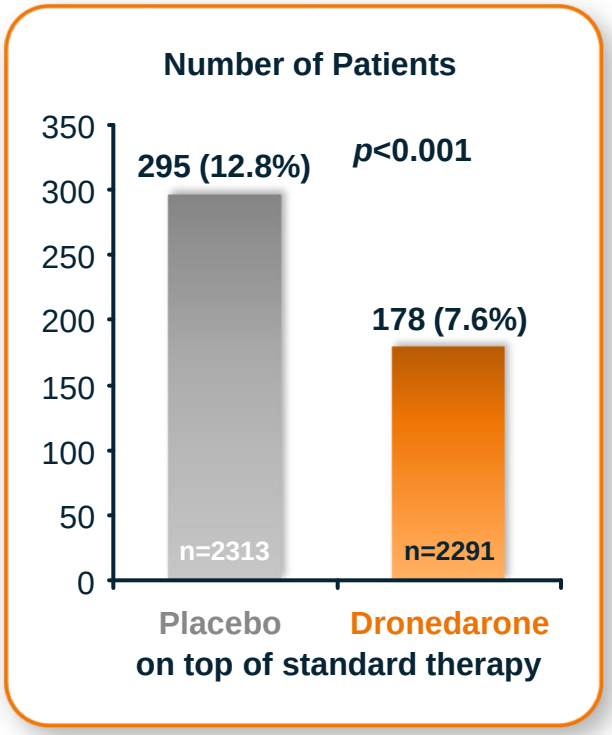
Time to 1st DCV



Time to 1st AF/AFL



No patients in "Permanent AF"



All AF related hospitalisation: HR = 0.626; 95% CI = [.54; .73]

First AF related hospitalisation: HR = 0.63; 95% CI = [.55; .72]

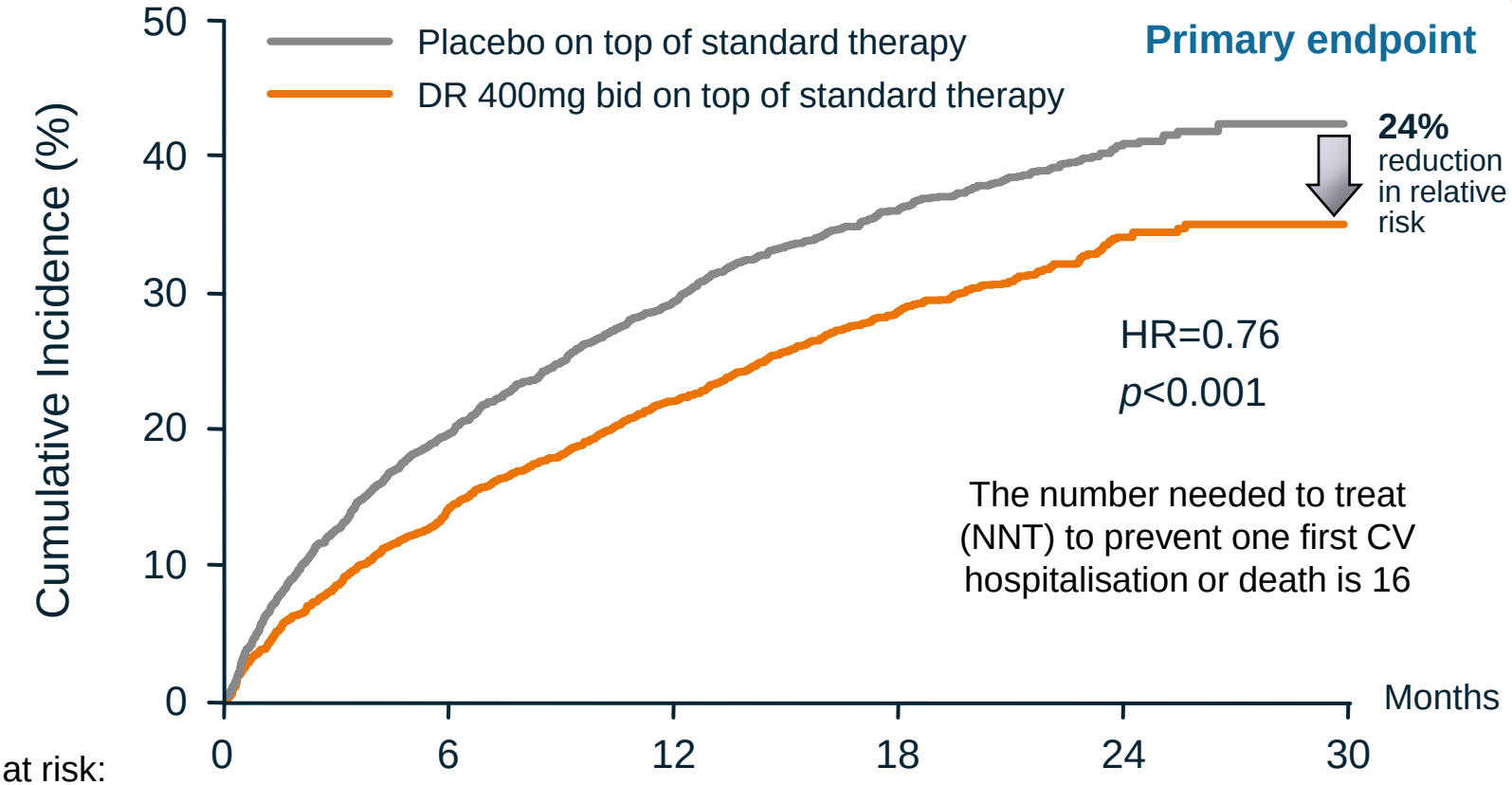
DCV=Direct cardioversion

Adapted from :

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

Page et al. Am J Cardiol. 2011;107 (7):1019-1022.

Dronedarone significantly decreased risk of unplanned CV hospitalisation or death from any cause by 24%



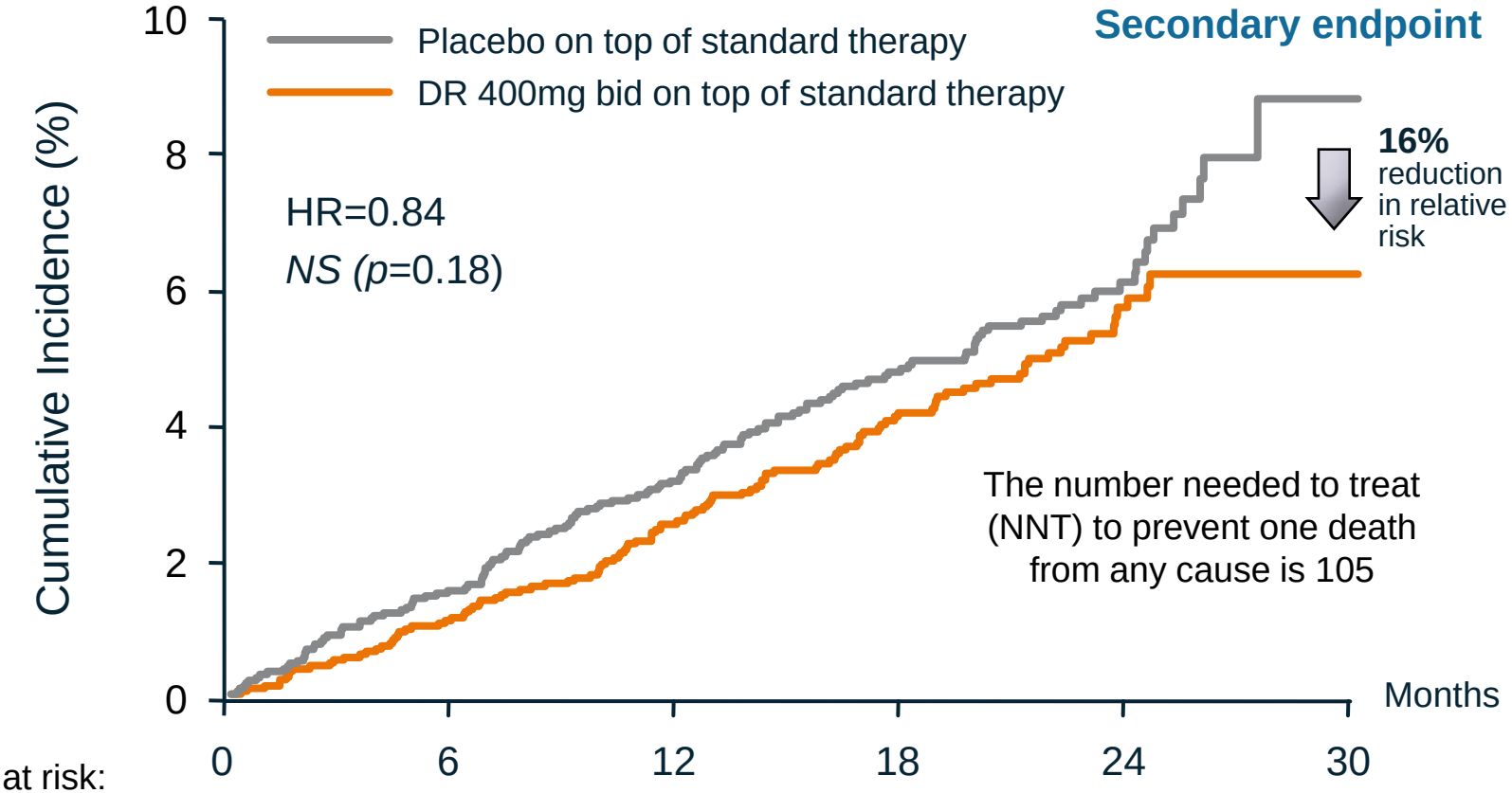
Patients at risk:

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

Adapted from:
Hohnloser SH, et al. N Engl J Med 2009;360:668-78.
EMA Assessment Report for Multaq. Page 32. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001043/WC500044538.pdf accessed 13/02/12

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

Dronedarone non-significantly reduced risk of all-cause death by 16%



Patients at risk:

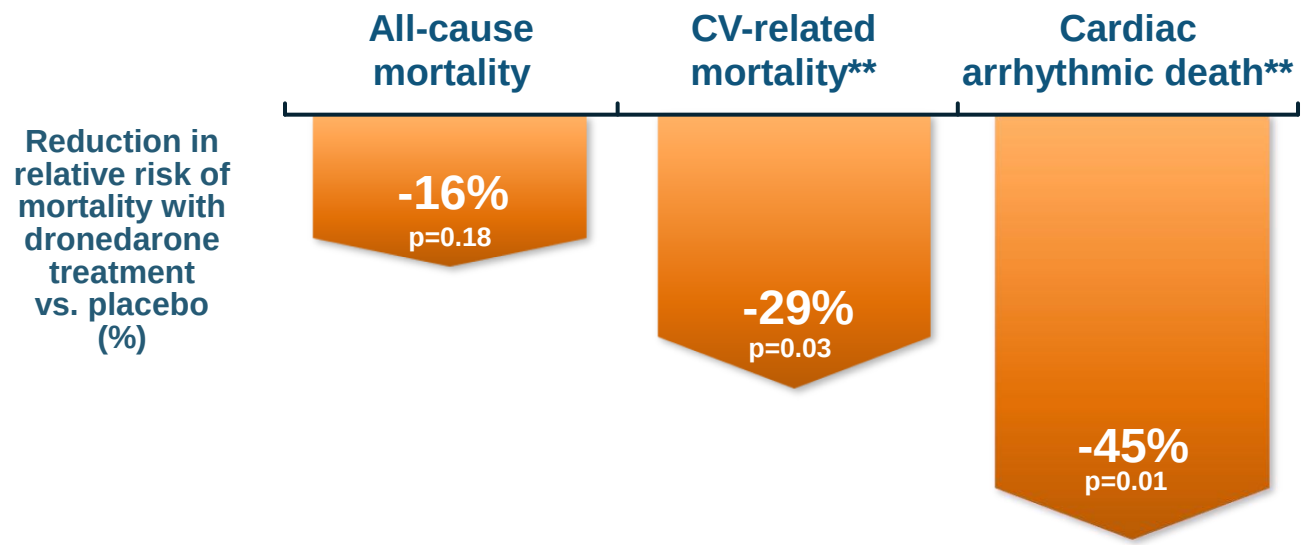
Placebo	2,327	2,290	2,250	1,629	636	7
DR 400mg bid	2,301	2,274	2,240	1,593	615	4

Mean follow-up 21 ±5 months.

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

Dronedarone significantly reduced the risk of CV-related mortality in AF patients

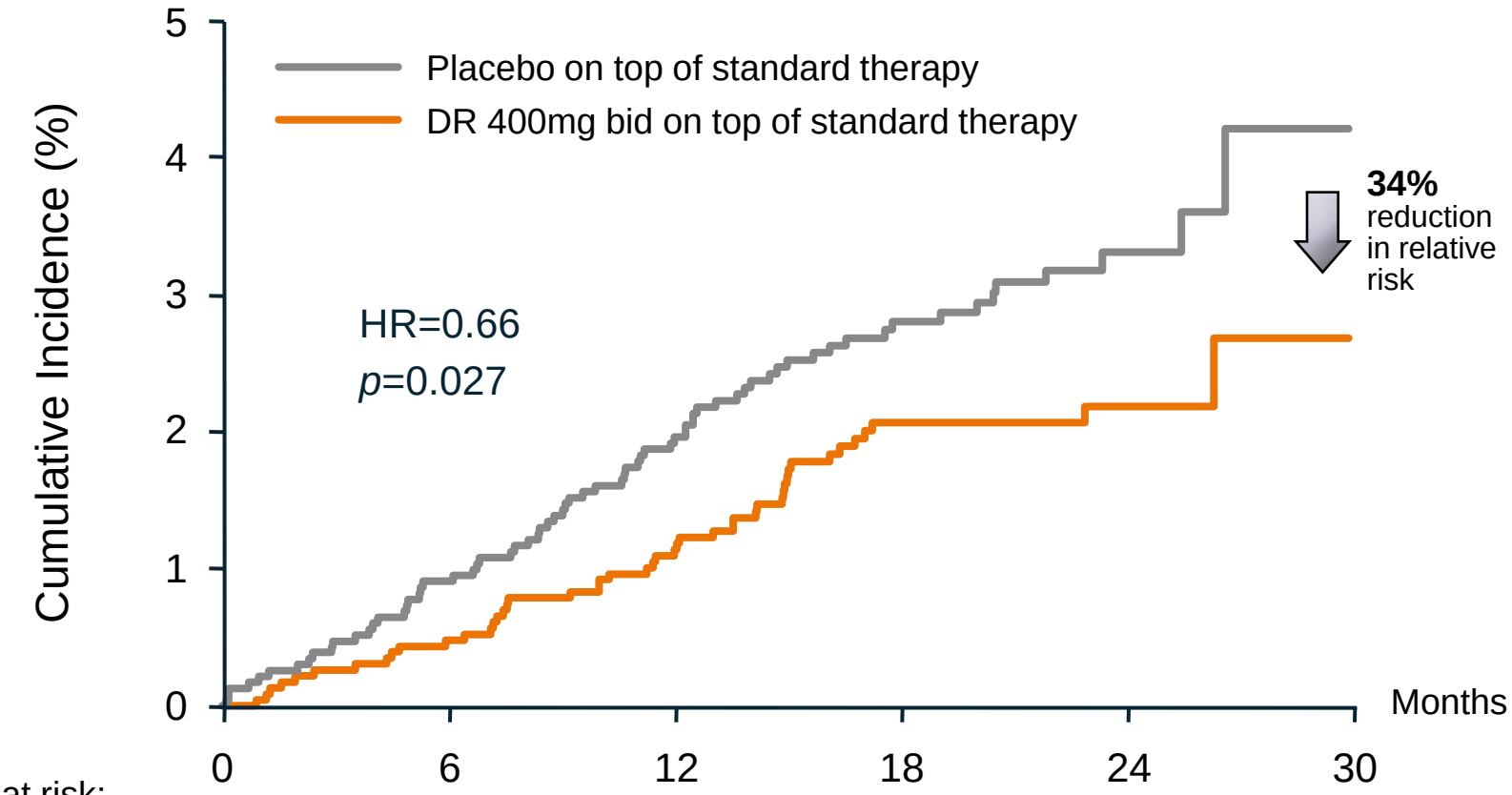
Secondary endpoints **Reduction in the relative risk of death (Dronedarone vs. placebo*)**



* Dronedarone and placebo treatments were additional to standard therapy
** CV and arrhythmic deaths were secondary endpoints

Adapted from Hohnloser SH, *et al.* N Engl J Med 2009; 360: 668–78

Dronedarone significantly reduced the relative risk of stroke by 34%



Patients at risk:

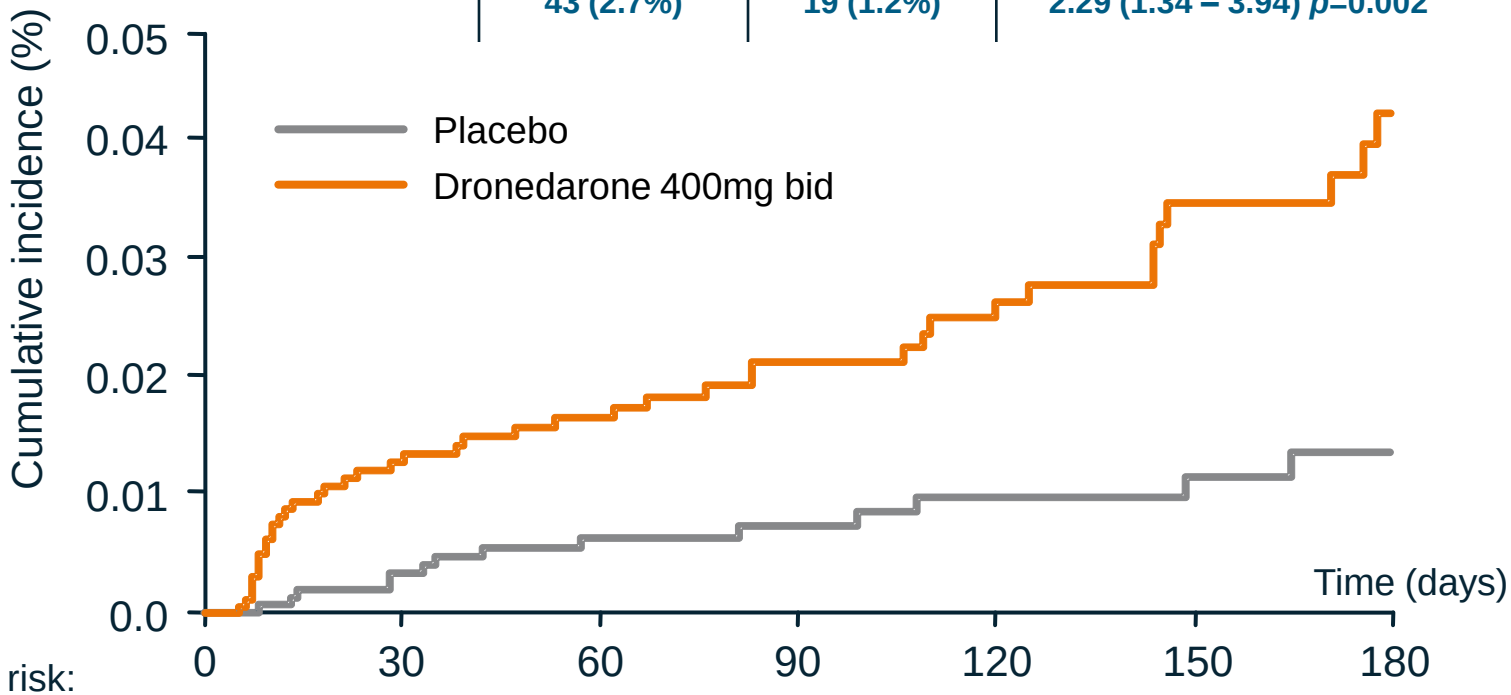
Placebo	2,327	2,275	2,220	1,598	618	6
DR 400mg bid	2,301	2,266	2,223	1,572	608	4

Mean follow-up 21 ±5 months.

Adapted from Connolly *et al; Circulation.* 2009;120:1174-1180.

PALLAS: first co-primary outcome (stroke, MI, SE, CV death)

First Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	43 (2.7%)	19 (1.2%)	2.29 (1.34 – 3.94) *p*=0.002



Number at risk:

Placebo	1,617	1,445	908		377
DR 400mg bid	1,619	1,421	930		353

Adapted from Connolly SJ *et al. N Engl J Med.* 2011; 365:2268-2276

Dronedarone: only AAD with monitoring regulations[1,2]

INDICATION

Dronedarone is indicated for the **maintenance of sinus rhythm** after **successful cardioversion** in **adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).**
Due to its safety profile (see sections 4.3 and 4.4), dronedarone should only be prescribed after alternative treatment options have been considered. Dronedarone should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

MONITORING

Patient should be monitored prior to and during dronedarone treatment
AF status: ECGs serially, at least every 6 months.
Heart failure, left ventricular function
Liver function tests should be performed prior and during treatment (after 1wk and 1mo following th. initiation; then repeated monthly for 6 mo, at 9. and 12. month, and periodically thereafter). If ALT levels are confirmed to be ≥3 × ULN after re-measurement, treatment with dronedarone should be withdrawn
Pulmonary function status : dronedarone should be discontinued if pulmonary toxicity is confirmed
Plasma creatinine values should be measured prior to and 7 days after initiation of dronedarone. If creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.
INR values in case of vitamin K antagonist therapy as per clinical AF guidelines.

CONTRA-INDICATIONS

Permanent AF with an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
Patients in unstable hemodynamic conditions
History of, or current heart failure or left ventricular systolic dysfunction
Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors
Patients with liver and lung toxicity related to the previous use of amiodarone
Severe hepatic impairment
Severe renal impairment (CrCl <30ml/min)
Co-administration with dabigatran

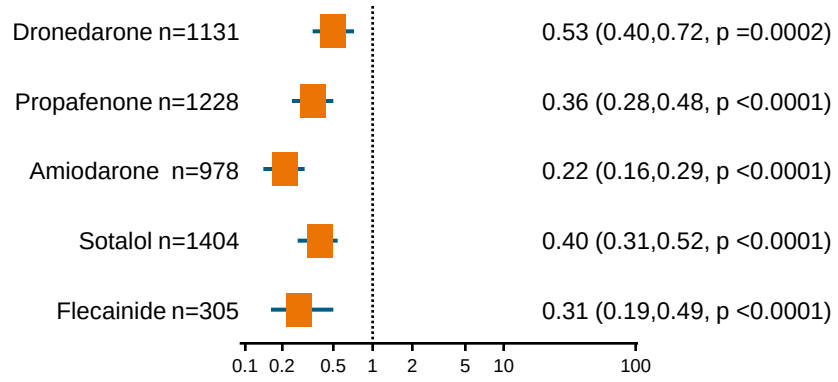
COUNCELLING

They should consult a physician if they develop signs or symptoms of heart failure;
They should immediately report to a physician any symptoms of potential liver injury;
They should consult a physician if they have breathlessness or non productive cough;
dronedarone interacts with a number of medicines;
If they consult other doctors they should inform them that they are taking dronedarone;
They should not take St John's Wort with dronedarone;
They should avoid grapefruit juice.

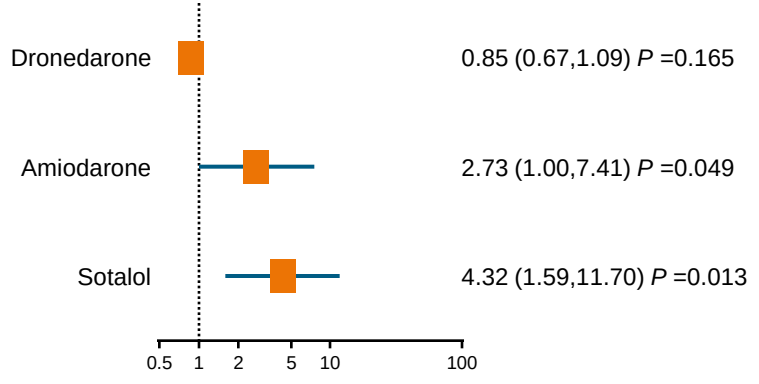
1,2 dronedarone SmPC xx, 2013., PIL xx, 2013.
Refer to dronedarone respective prescribing information for full list of contraindications and other prescribing

AADs: safety and efficacy comparison based on a mixed treatment analysis

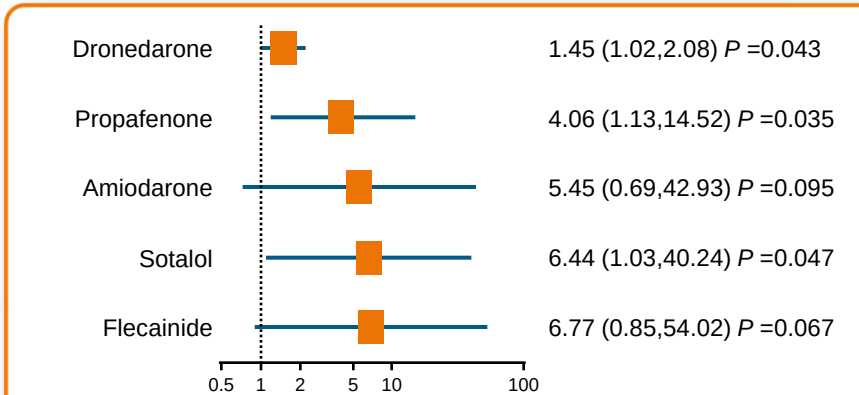
Efficacy (AF recurrence)*



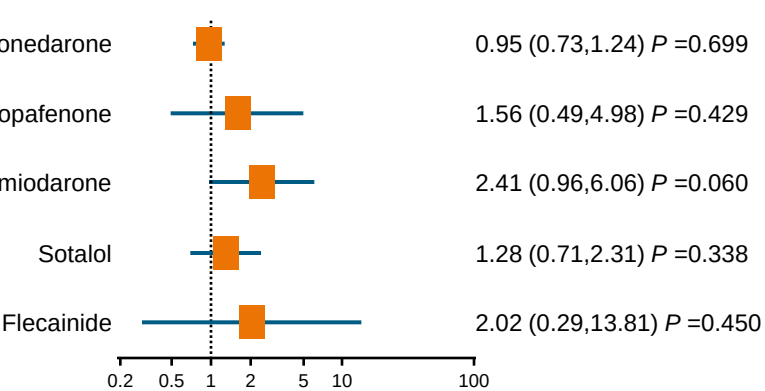
All-cause mortality*



Proarrhythmic events*,†



Serious adverse events*



*versus placebo

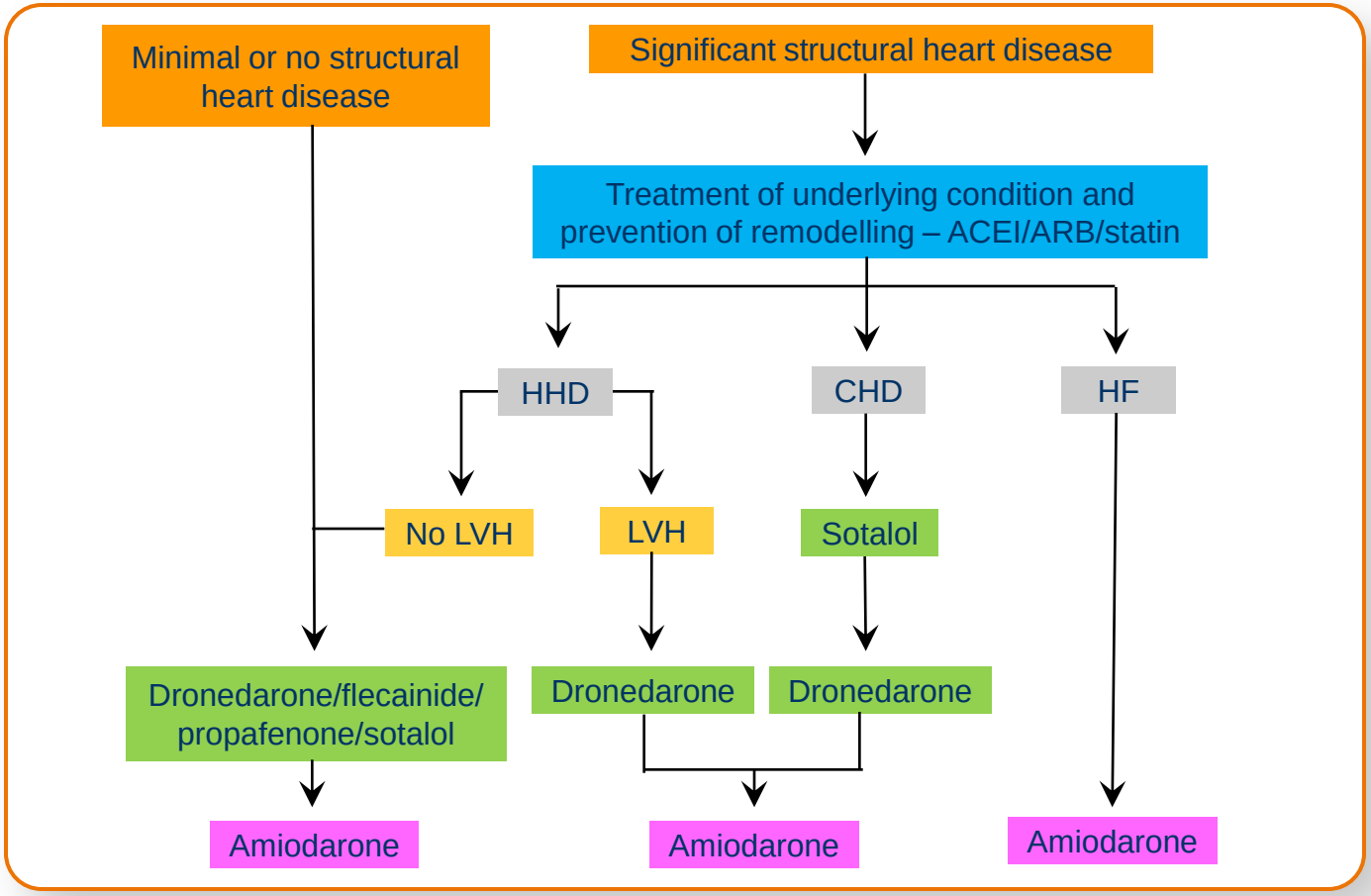
†Proarrhythmic events includes bradyarrhythmia

Odds ratios and 95% confidence intervals

Adapted from Freemantle N, *et al. Europace* 2011;13(3):329-45.

What changed in 2012?

Choice of antiarrhythmic drug according to underlying pathology



- MULTAQ® should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure. Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with MULTAQ® should be discontinued.
- MULTAQ® should be used with caution in patients with coronary heart disease.

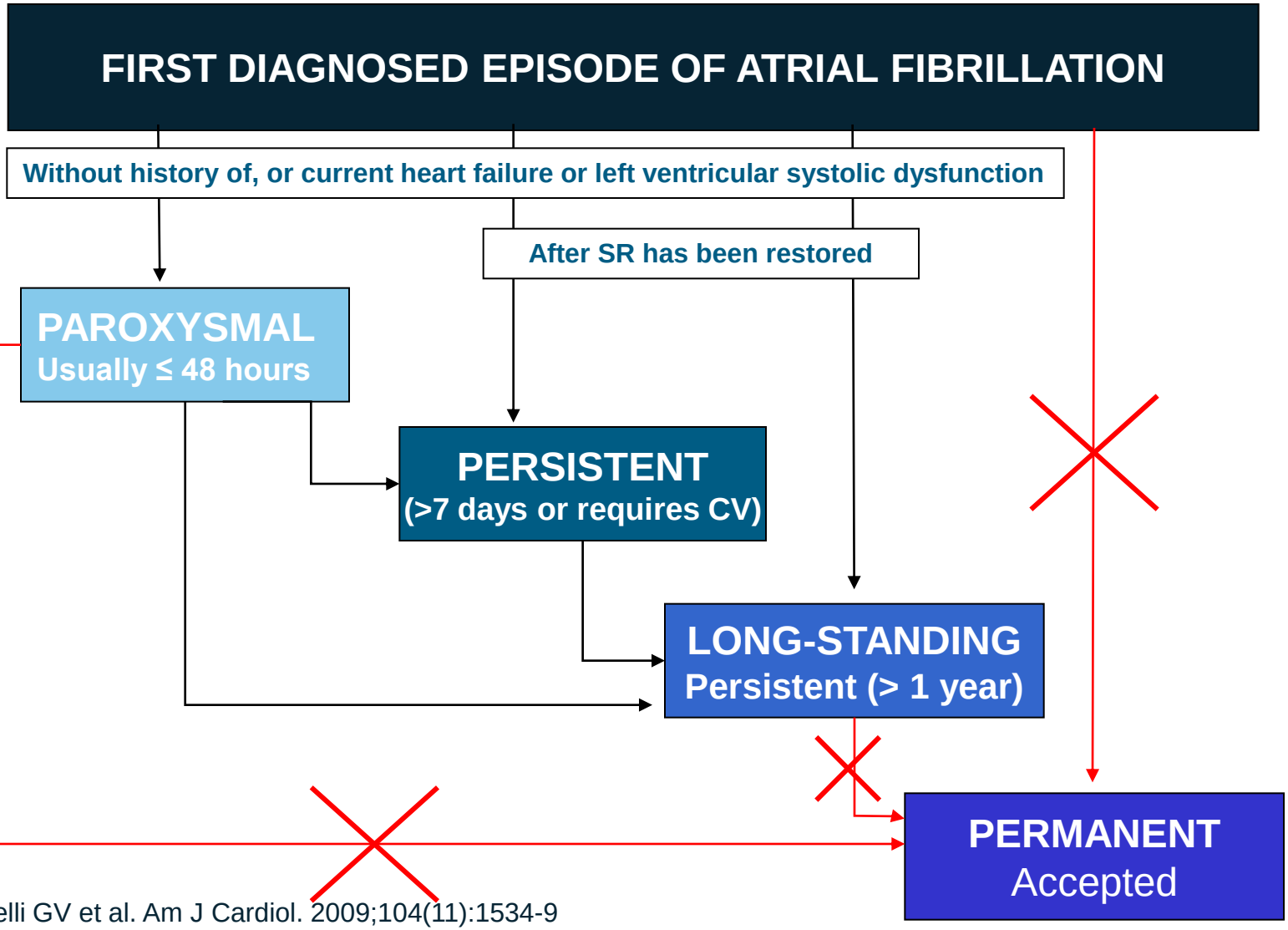
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CHD, coronary heart disease; HF, heart failure; HHD, hypertensive heart disease; LVH, left ventricular hypertrophy.

Camm AJ, et al.
Eur Heart J. 2012;33:2719-47.

....back to the facts and dronedarone

- **Progressive disease**
- **RRR of all-cause death - 16% (NS), but....**
- **RRR of stroke - 34%**
- **significantly lower vs. placebo**
- **favorable maintanance of sinus rhythm**

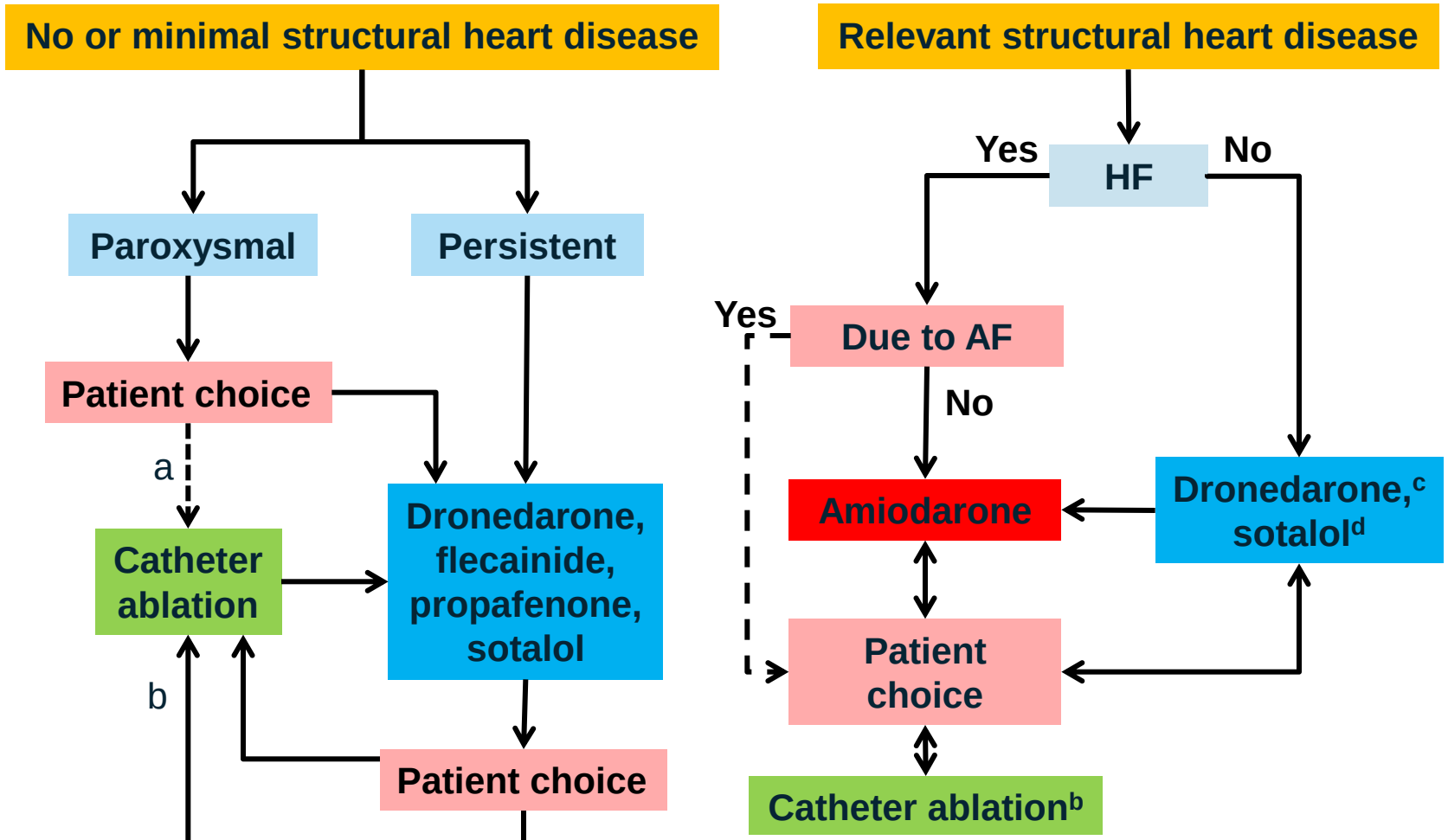
Dronedarone is indicated for ~40% of total AF Population[1,2]



1. Naccarelli GV et al. Am J Cardiol. 2009;104(11):1534-9
2. Levy, S Maarek M, Coumel P, et al., Characterisation of different subsets of atrial fibrillation in general practice in France: the ALFA study, Circulation, 1999;99:3028-35.

AADs and / or left atrial ablation for rhythm control in AF

Version 2012 ESC Guidelines for AF Management



a = Usually pulmonary vein isolation is appropriate
b = More extensive left atrial ablation may be needed
c = Caution with coronary heart disease
d = Not recommended with LVH
Heart failure due to AF = tachycardiomyopathy.

Adapted from Camm AJ, et al. Eur Heart J. 2012;33:2719-47.

Typical indications for dronedarone:

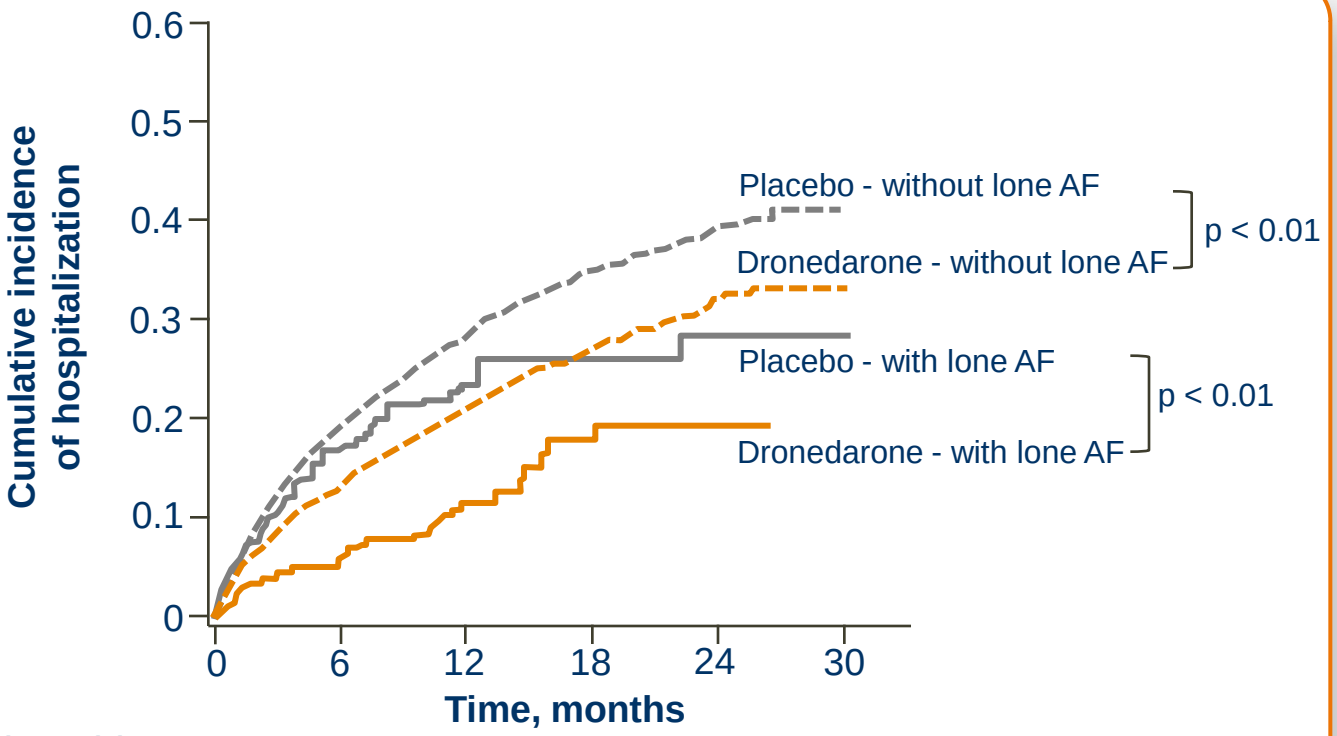
- lone AF‘ patients
- younger patients
- patients with hypertension
- patients with CHD, without HF
- atrial ablation

What’s new in 2013?

- New data from clinical studies
- Real-life data with dronedarone
- Translating guidelines into clinical practice

Dronedarone in patients with lone AF

Pooled analysis from ATHENA/EURIDIS/ADONIS on first CV hospitalization (secondary)



Number at risk

Placebo - without lone AF	2,532	1,977	1,709	1,025	359	2
Placebo - with lone AF	192	130	108	40	23	1
Dronedarone - without lone AF	2,881	2,341	2,072	1,121	380	2
Dronedarone - with lone AF	240	197	167	52	22	0

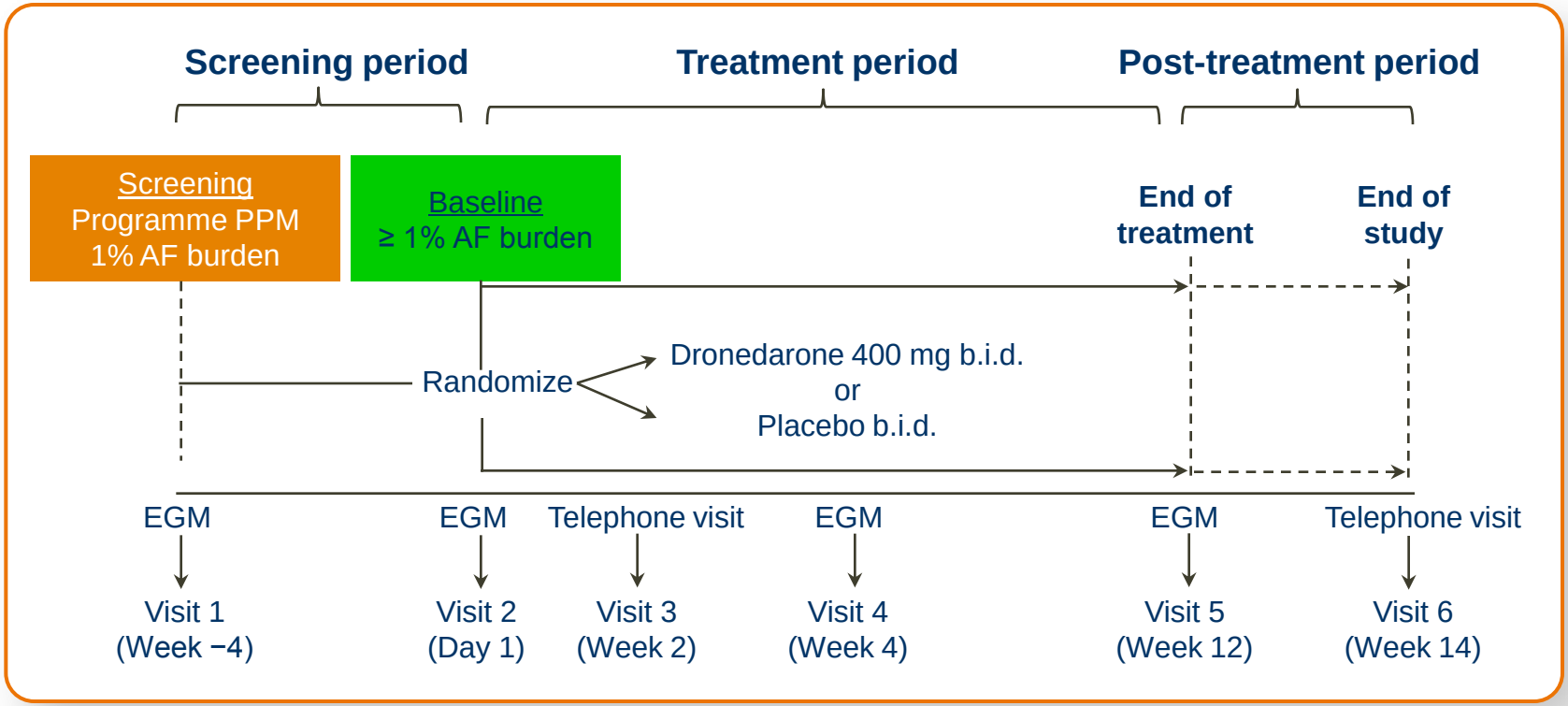
The enrolled AF population in the ATHENA study is broader than the indicated population for dronedarone.

CV, cardiovascular.

Duray GZ, et al. J Cardiovasc Electrophysiol. 2011;22:770-6.

HESTIA trial

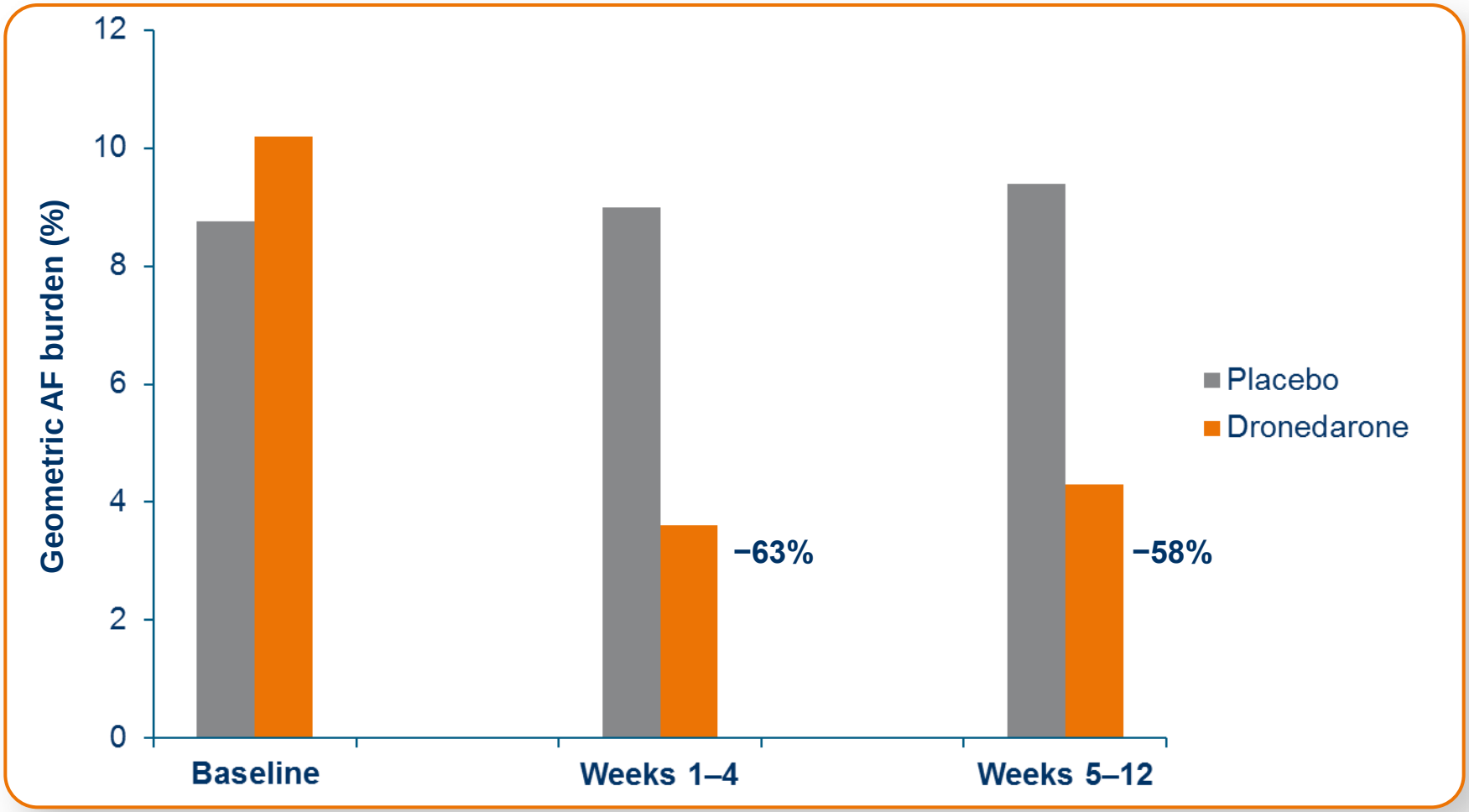
Aim: to evaluate the effects of dronedarone on AF burden in patients with dual-chamber pacemakers



ClinicalTrials.gov NCT 01135017 (Available from www.clinicaltrials.gov. Accessed August 2013).
Ezekowitz MD, et al. Circulation. 2012;126:A15020. Poster presented at AHA 2012.

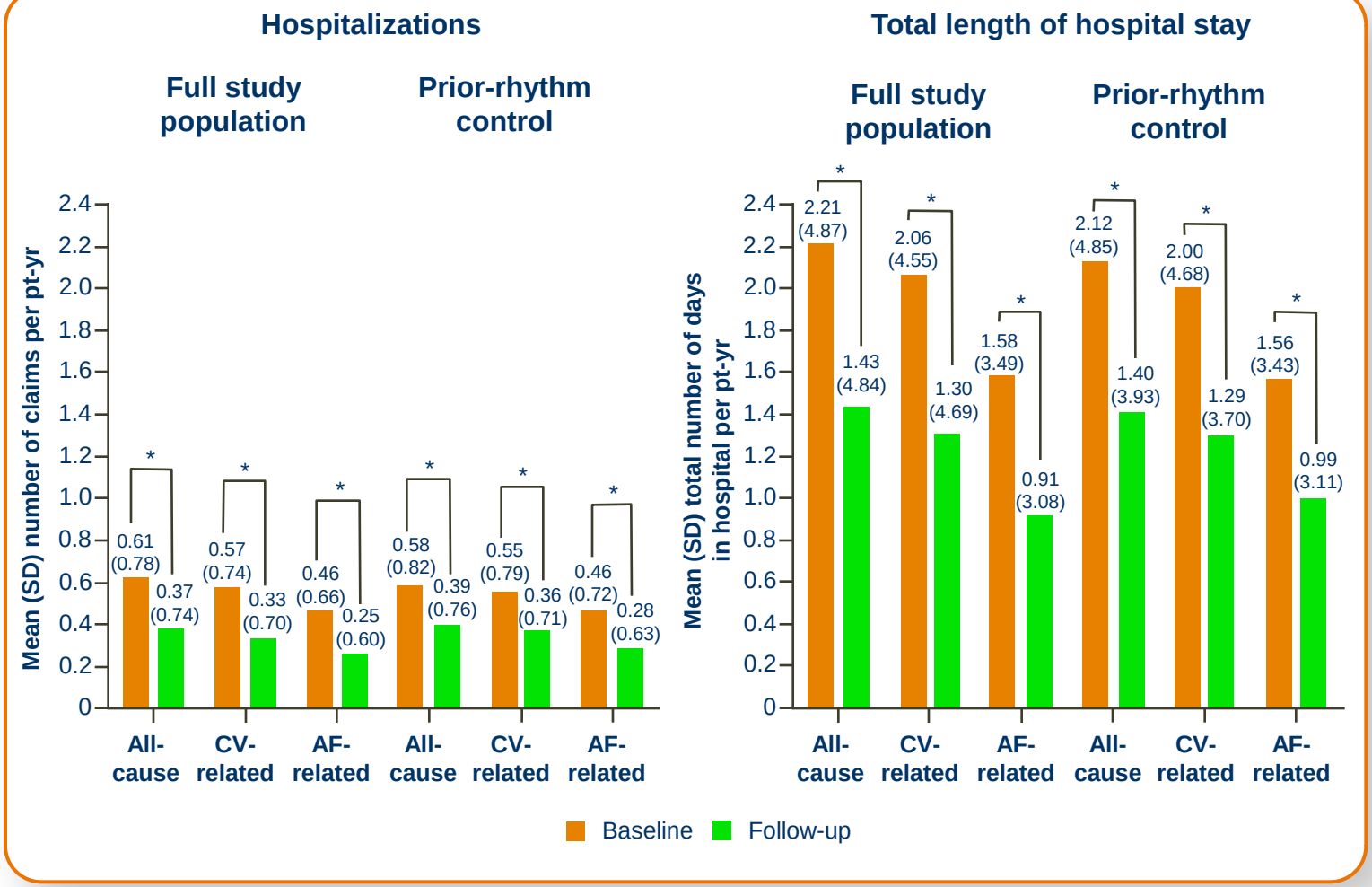
EGM, electrogram; PPM, permanent pacemaker.

Changes (%) in AF burden induced by dronedarone



ClinicalTrials.gov NCT 01135017 (Available from www.clinicaltrials.gov. Accessed August 2013).
Ezekowitz MD, et al. Circulation. 2012;126:A15020.
Poster presented at AHA 2012.

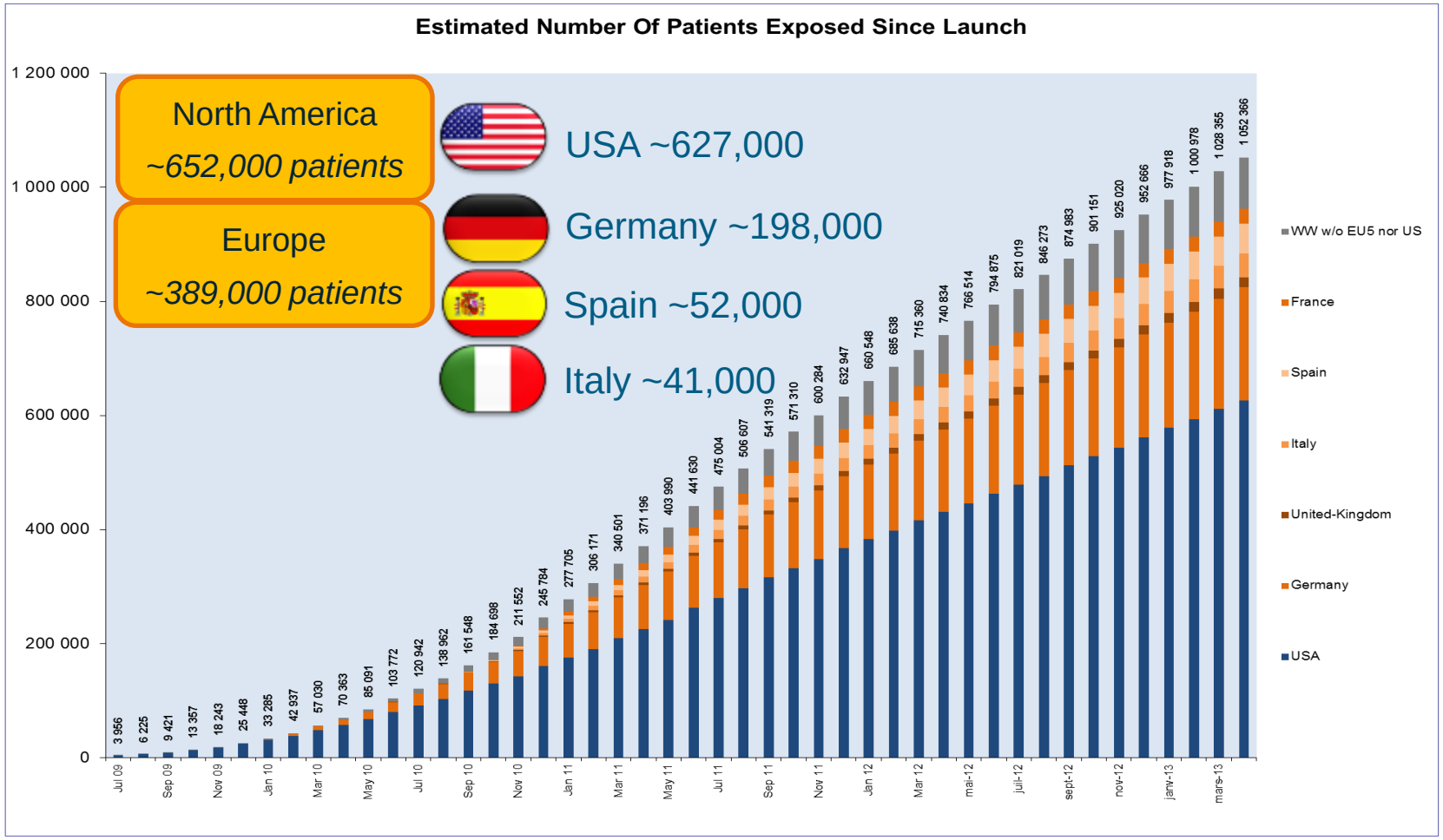
Effectiveness of dronedarone among US patients with AF/AFL in a real-world setting



* p < 0.0001, intra-group comparison of baseline versus follow-up periods.
pt-yr, patient-year.

Kim MH, et al. Circ Cardiovasc Qual Outcomes. 2013;6:A140.

~1,052,366 patients have received treatment with dronedarone worldwide since July 2009[1]



1. Cumulative number of patients. Estimated. IMS/MIDAS Worldwide Monthly Database, Standard Units Sold up until 30 April 2013. For some countries, latest data available is from October and has been used for the calculation of the total.

Sinus rhythm is „God given”...

…I WAS BORN IN SINUS RHYTHM – AND I DON'T WANT TO DIE IN ATRIAL FIBRILLATION

Ronald Campbell, John Camm