ATHENA

- A new drug’s trial

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.

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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)

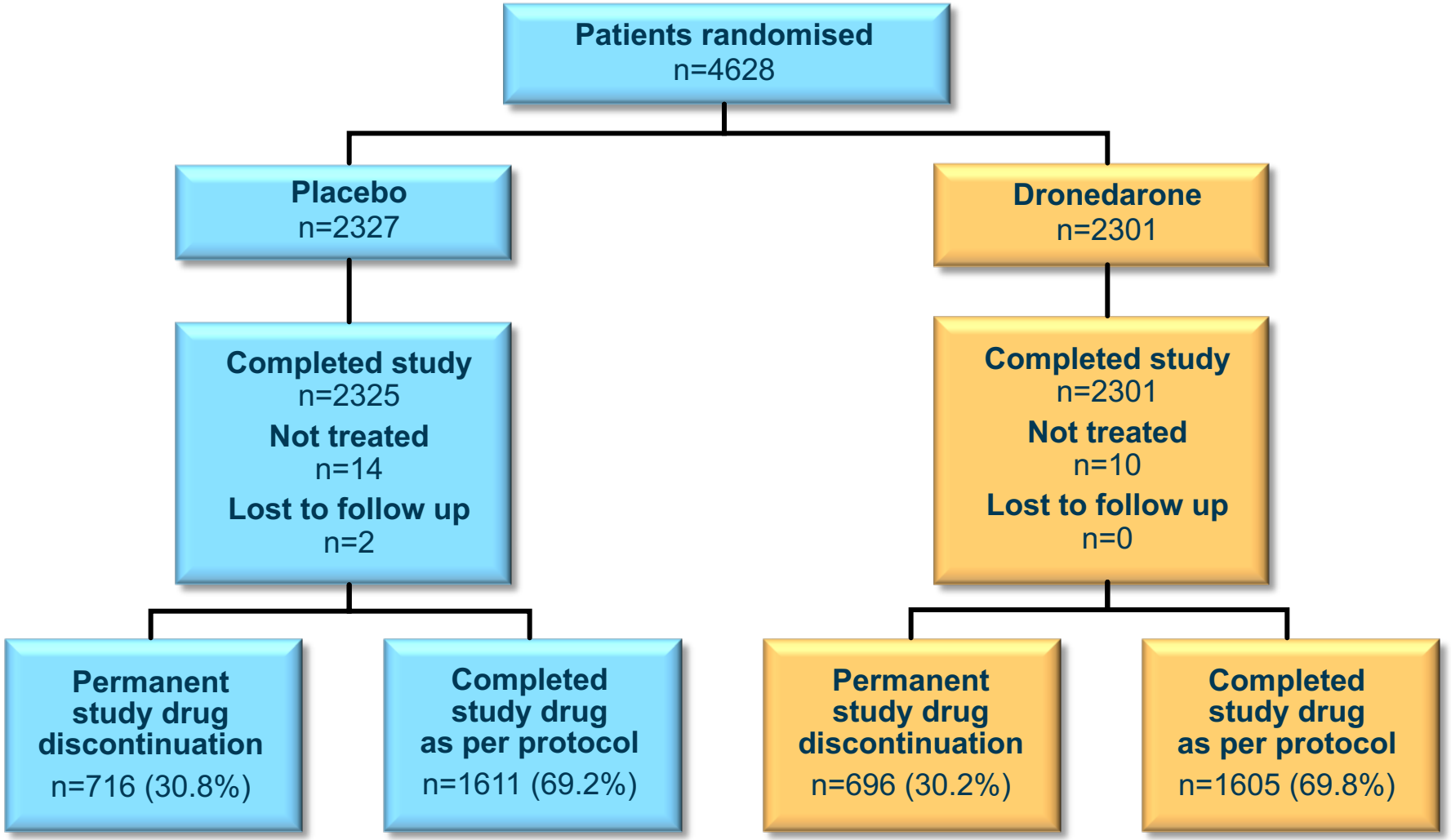
- **Originally the protocol had allowed patients <70 years of age with additional risk factors into the study**
- **The protocol was subsequently amended to include only patients ≥70 years of age**

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.

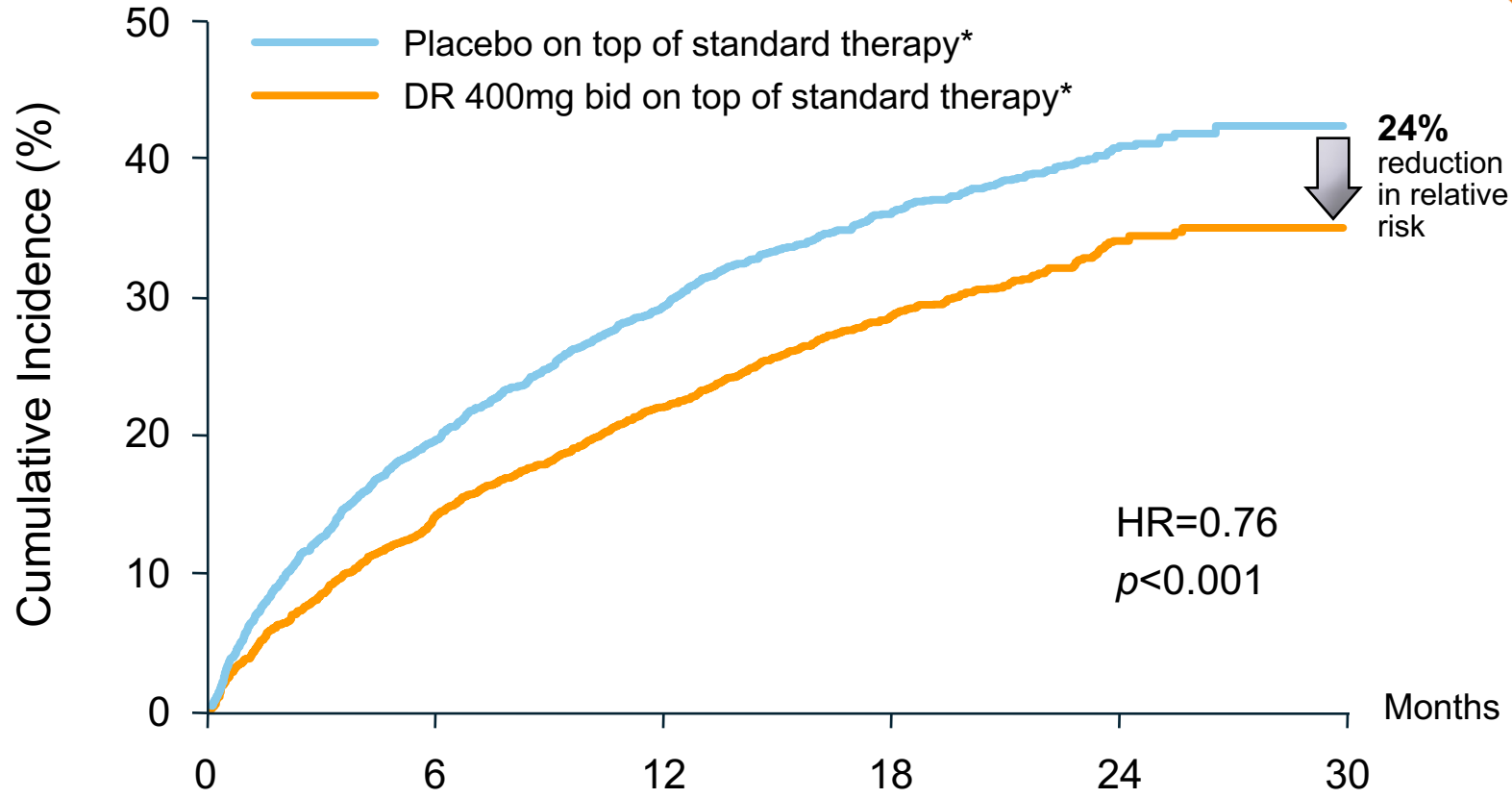
Concomitant Medications

		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%

ATHENA



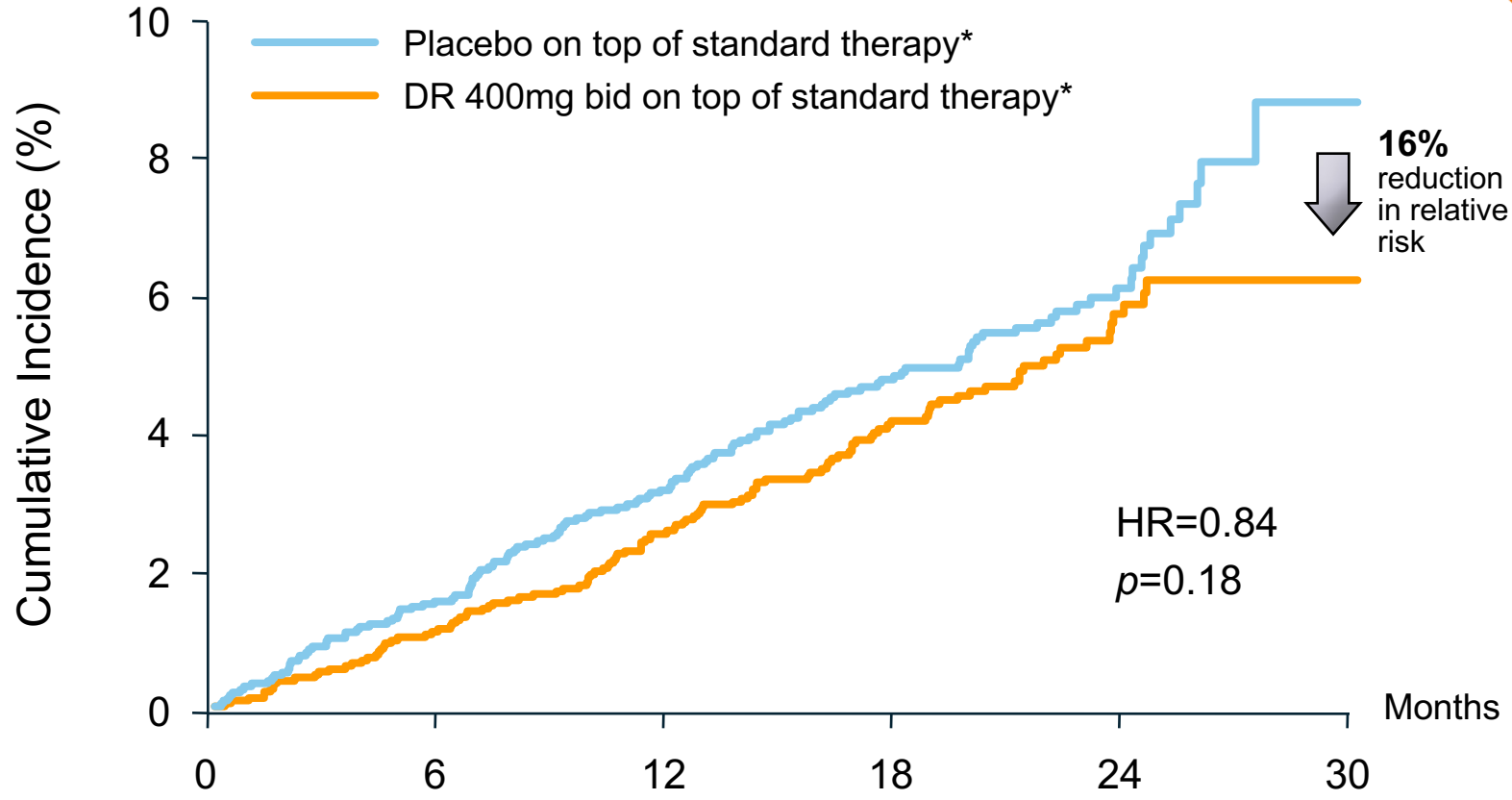
Patients at risk:

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

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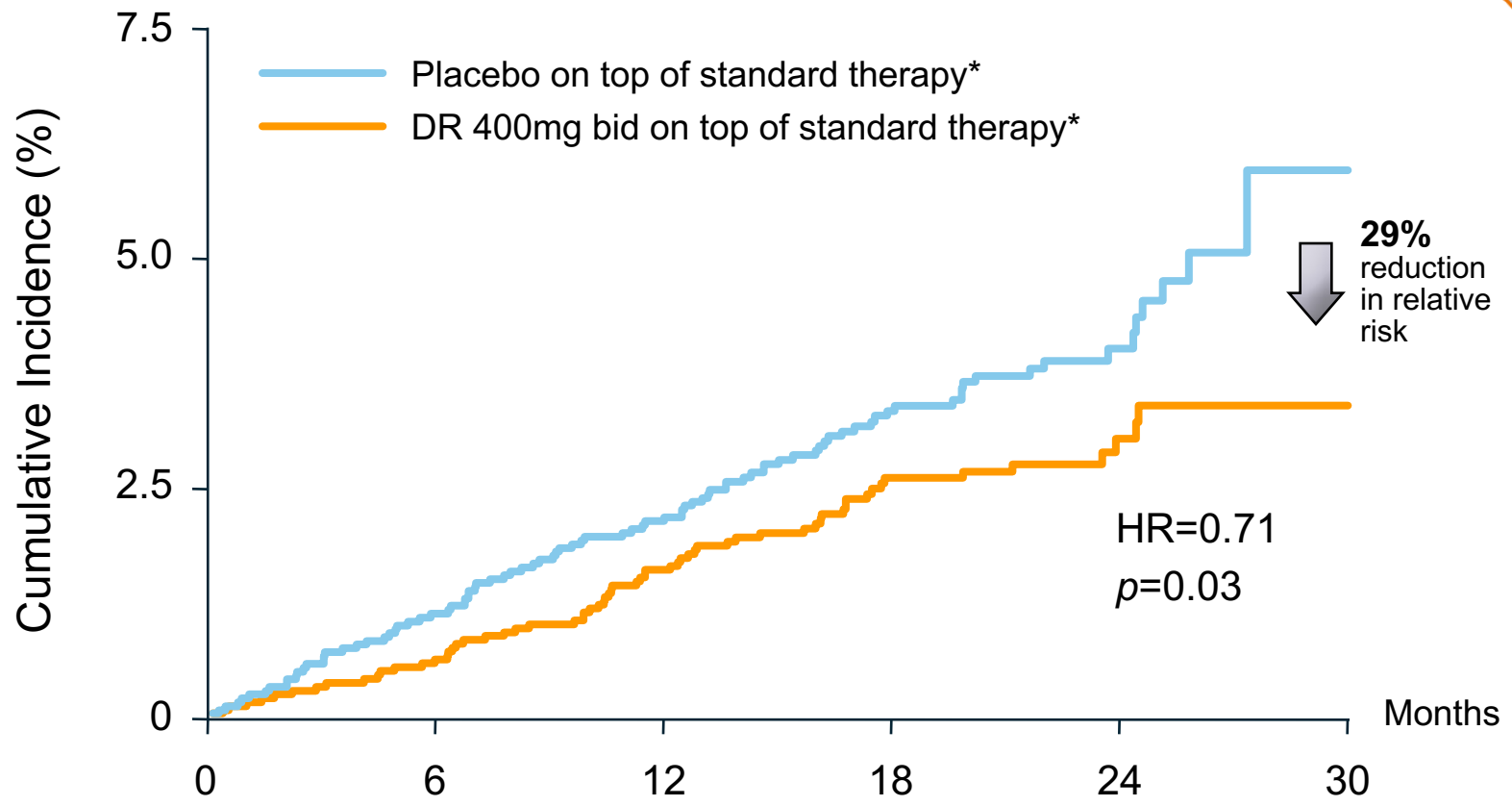
Mean follow-up 21 ±5 months.

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

Dronedarone Significantly Decreased Risk of 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**

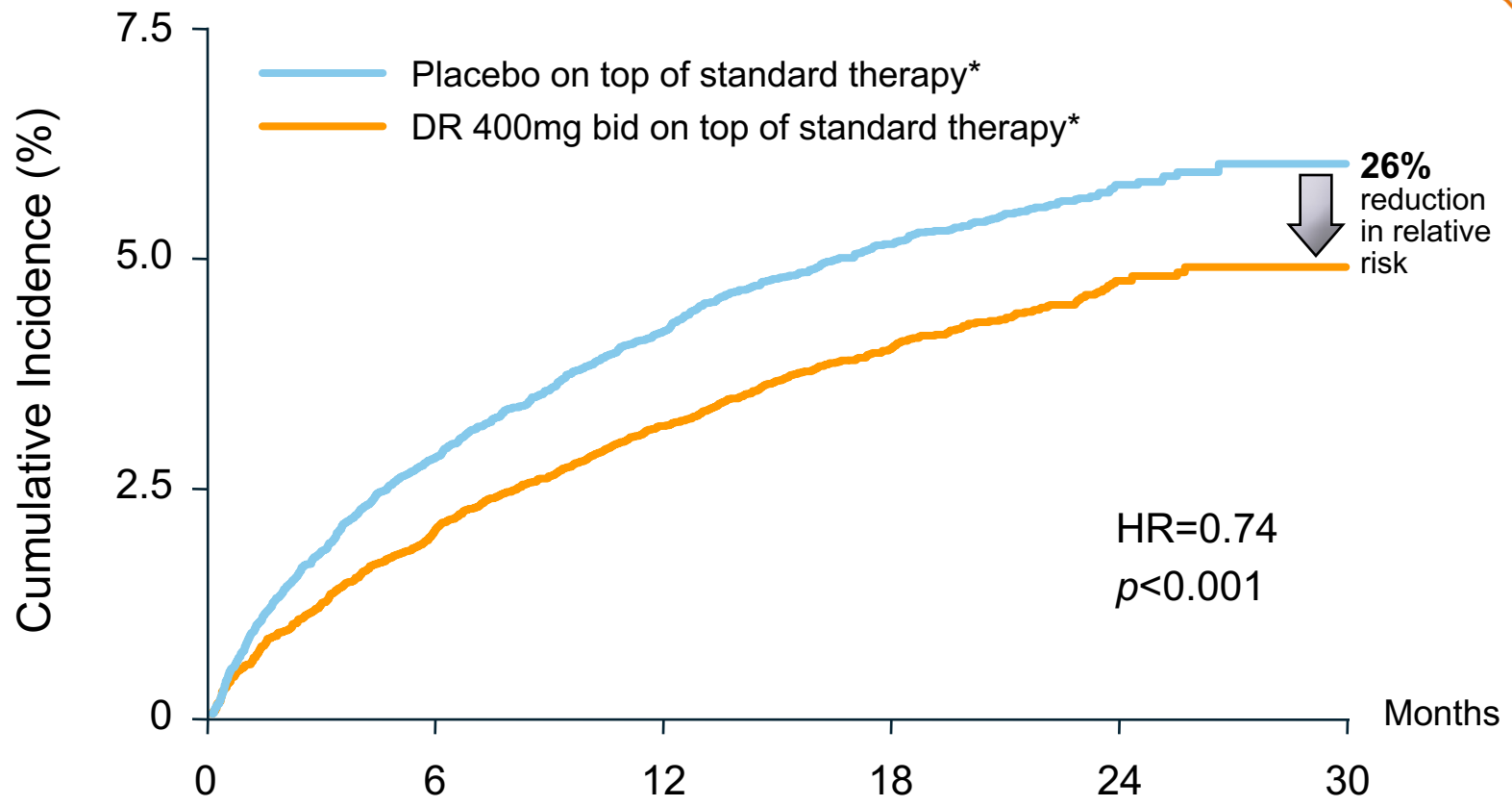
Hohnloser SH *et al. N Engl J Med 2009;360:668-78.*

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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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