

ATHENA

► A new drug's trial

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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 - 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

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.

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ATHENA is a unique trial in several ways:

With more than 4,600 patients, it is the largest single antiarrhythmic drug trial ever conducted in AF

ATHENA used unique endpoints for an AF trial ie CV hospitalization or death

Reference

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.

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A number of measures have been used to gauge the success of AAD therapy. Time to first recurrence of AF, any AF recurrence, AF burden (total percentage of time a patient has AF as determined by the number and duration of AF episodes), and a reduction in symptoms are the most commonly used measures of success.

None of these soft endpoints has demonstrated to be a valid surrogate to CV outcomes

Reference

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.

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AF has a complex aetiology and causes morbidity and mortality through different mechanisms

Hence assessment of outcomes in all major domains of AF-related morbidity and mortality is desirable for any clinical trial in AF

Reference

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.

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ATHENA was a double-blind, randomised, multinational trial designed to 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 over a minimum treatment and follow-up duration of 12 months in patients with paroxysmal or persistent AF/AFL

Patients in both arms were receiving standard therapy. 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 cardiovascular agents such as ACEIs/ARBs and statins.

Reference

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.

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The primary composite endpoint was cardiovascular hospitalisation and all-cause mortality

The secondary endpoints were death from any cause, cardiovascular death and hospitalisation for cardiovascular reasons

Reference

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

Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> 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) 	<ul style="list-style-type: none"> 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

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

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

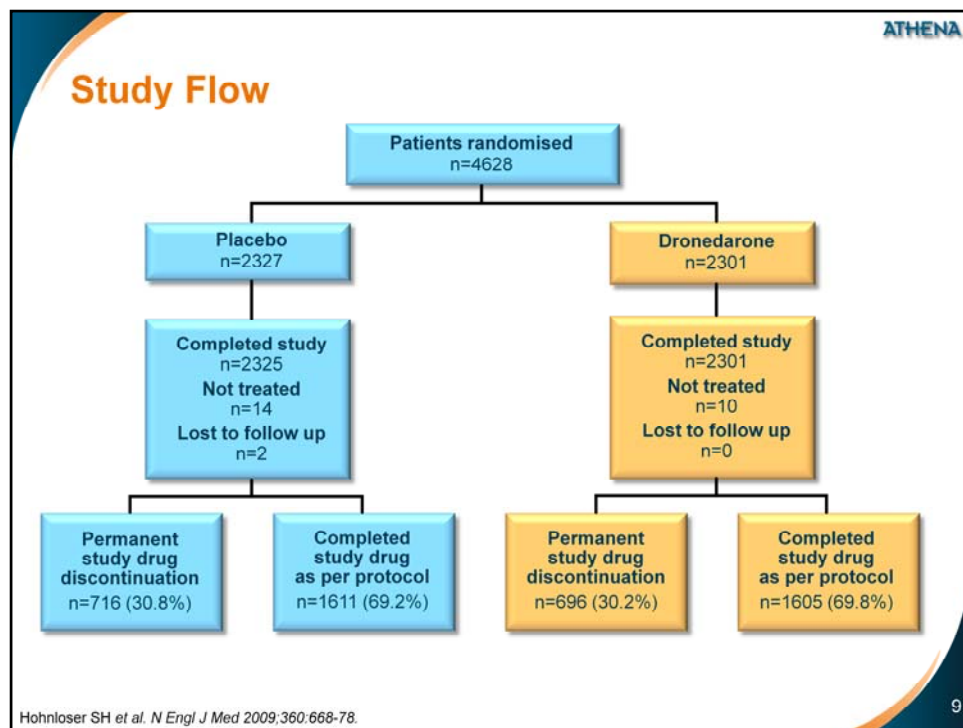
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Patients were either ≥ 75 years (with or without cardiovascular risk factors) or ≥ 70 years and ≥ 1 risk factor (hypertension; diabetes; prior stroke/TIA; LA ≥ 50 mm; LVEF < 0.40)

The protocol originally allowed patients < 70 years of age with additional risk factors into the study but was amended to include only patients ≥ 70 years of age as described above. This means that the study population contains a large proportion of patients under 70

Reference

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



A total of 4,628 patients were randomised to receive dronedarone or placebo

Reference

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

Baseline Patient Characteristics

	Placebo n=2327	Dronedaron n=2301	All patients n=4628
Age (mean \pm SD, years)	71.7 \pm 9.0	71.6 \pm 8.9	72 \pm 9.0
<65yr	442 (19.0%)	431 (18.7%)	873 (18.9%)
65 to 75yr	907 (39.0%)	923 (40.1%)	1830 (39.5%)
\geq 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.

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Among the patients included in ATHENA,

86.3% had hypertension, which was the most prevalent underlying cardiovascular disease

30.4% had a history of coronary disease

21.2% had a history of heart failure

Therefore, the patients enrolled in ATHENA were representative of the general AF population

Reference

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

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

Concomitant Medications

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

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

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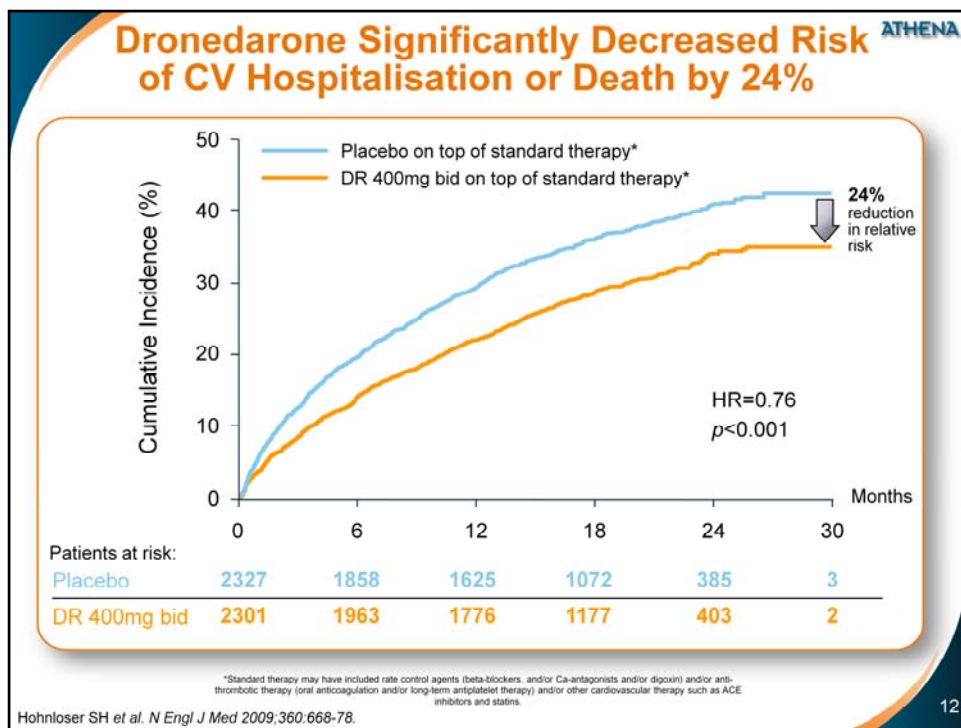
The benefit of dronedarone was obtained on top of standard background therapy, which may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and /or aspirin and other antiplatelets therapy) and/or other cardiovascular agents such as ACEIs/ARBs and statins

About equal proportions of the 2,301 patients randomised to dronedarone and the 2,327 patients in the placebo group were on betablockers, calcium channel blockers, ACE inhibitors, or angiotensin-receptor blockers, digoxin, statins, or oral anticoagulation

Reference

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

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

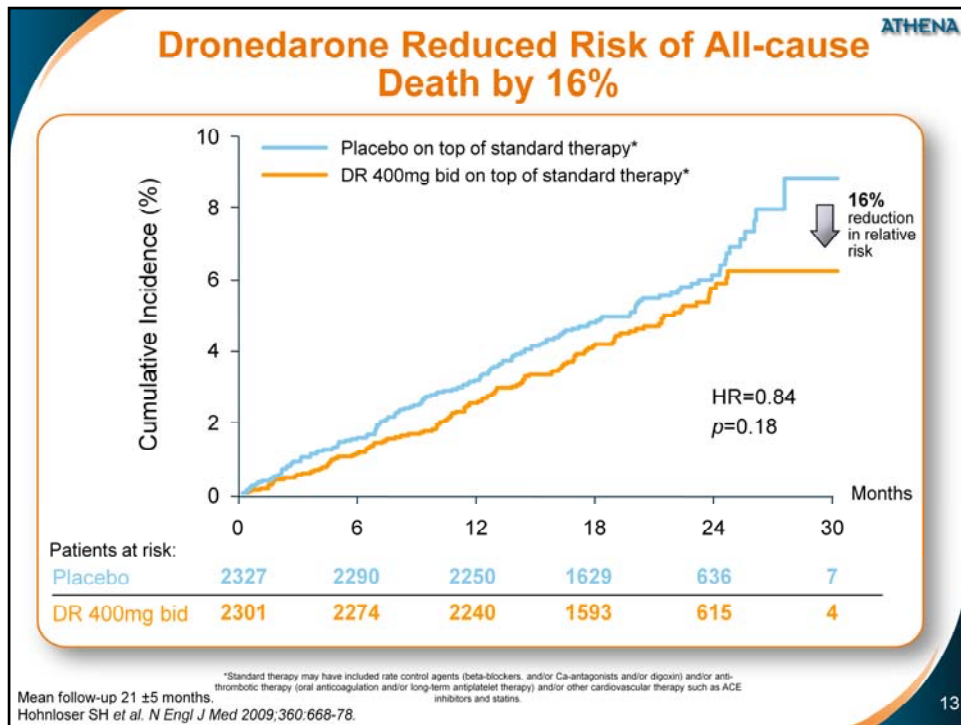


Dronedarone significantly decreased the risk of cardiovascular hospitalisations or death from any cause by 24% ($p<0.001$), meeting the primary study endpoint

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 cardiovascular agents such as ACEIs/ARBs and statins

Reference

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

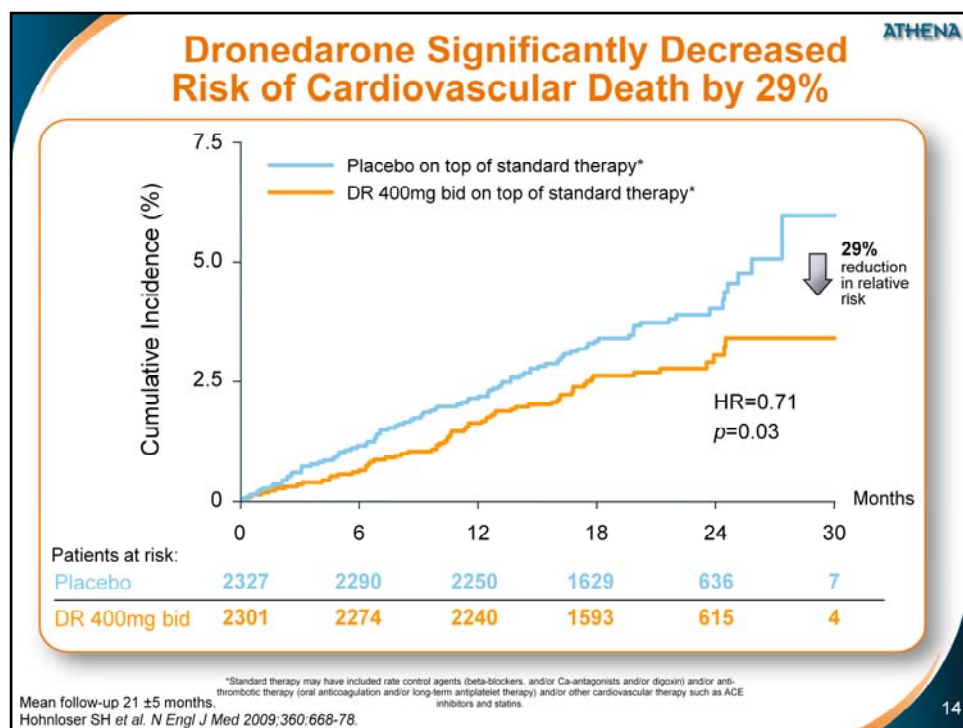


There were numerically fewer deaths (relative risk reduction of 16%) from any cause in the Dronedaronone group compared to placebo, but the result was not significant

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 cardiovascular agents such as ACEIs/ARBs and statins

Reference

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



Dronedarone significantly decreased the risk of cardiovascular death by 29% (p=0.03) on top of standard therapy, including rate control and antithrombotic drugs

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 cardiovascular agents such as ACEIs/ARBs and statins

Reference

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

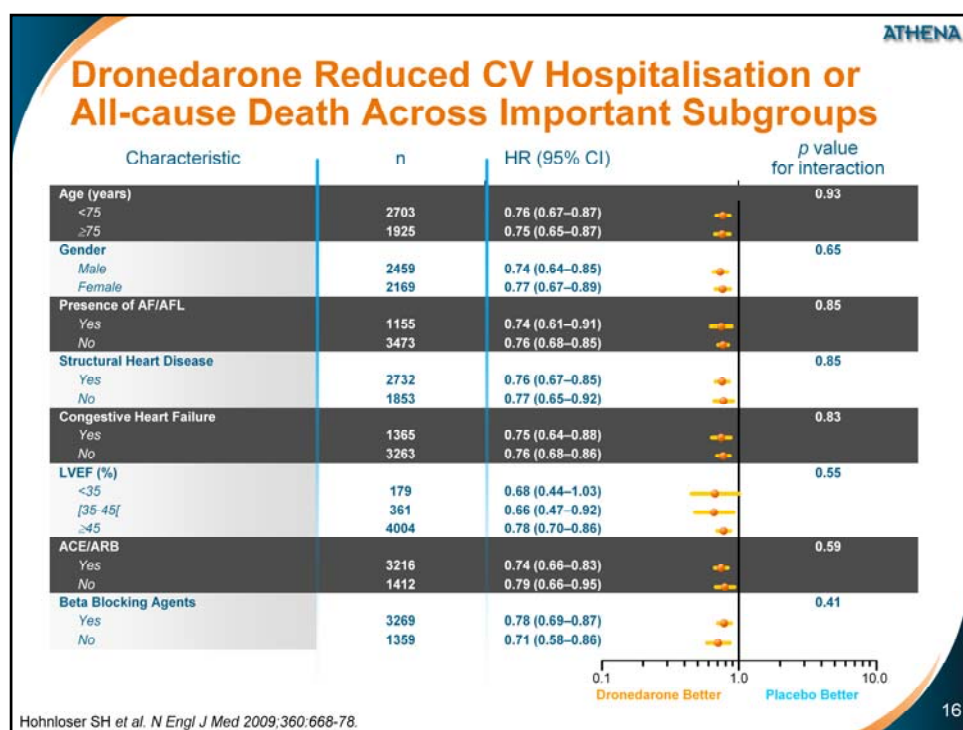
Hohnloser SH et al. *N Engl J Med* 2009;360:668-78.

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Along with the significant decrease in cardiovascular death (29%; $p=0.03$), Dronedarone also significantly decreased the risk for arrhythmic death, or sudden death, by 45% ($p=0.01$)

Reference

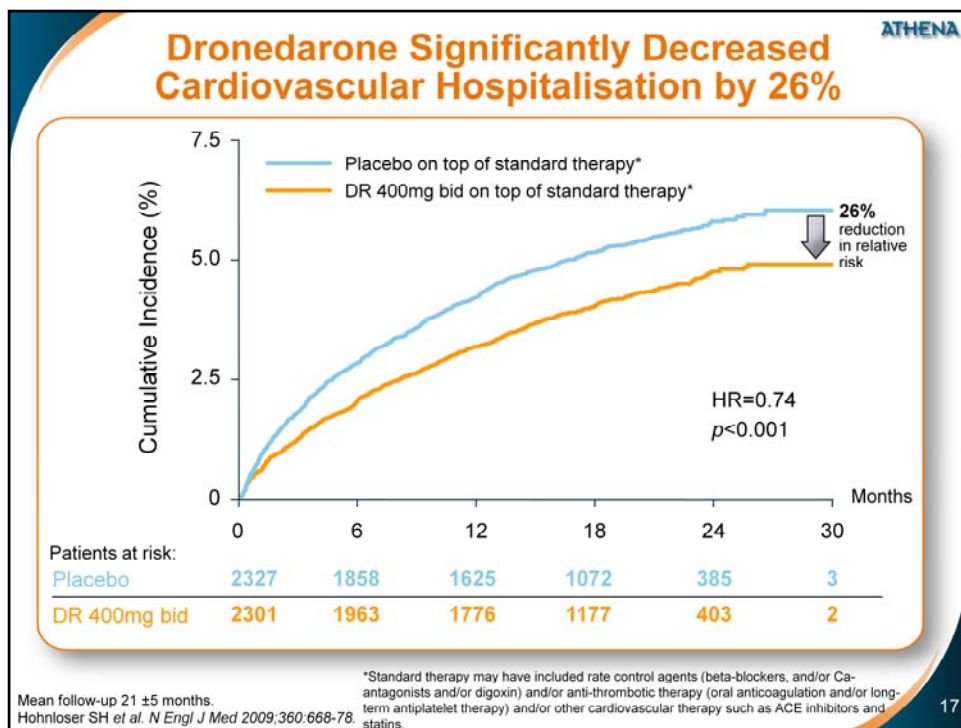
Hohnloser SH et al. *N Engl J Med* 2009;360:668-78.



Results of the primary endpoint were consistent across all the prespecified important subgroups

Reference

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



The first cardiovascular hospitalisation was reduced by 26% ($p<0.001$) in the Dronedarone group compared to placebo

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 cardiovascular agents such as ACEIs/ARBs and statins

Reference

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

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.

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Dronedarone reduced the incidence of all CV-related first hospitalisation by 26% ($p < 0.001$)

Post-hoc analysis examined the specific reasons for CV hospitalisation.

Hospitalisations related to AF were reduced by 37% ($p < 0.001$)

Reference

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

ATHENA

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

Randomised and treated patients	Placebo n=2313	Dronedaron 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.

The most common adverse events in the dronedarone arm were:

- Cardiac events, mainly bradycardia (3.5% in dronedarone group vs 1.2% in placebo group, $p<0.001$)
- QT-interval prolongation (1.7% vs 0.6%, $p<0.001$)
- Gastrointestinal, mainly diarrhea (9.7% vs 6.2%, $p<0.001$) and Nausea (5.3% vs 3.1%, $p<0.001$)
- Skin-related events, mainly rash (3.4% vs 2.0%, $p=0.006$)
- Serum creatinine increase (4.7% vs 1.3%, $p<0.001$). The serum creatinine increase may not be indicative of renal dysfunction as the glomerular filtration rate is unaffected

Reference

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
- ▶ Dronedaronone 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
- ▶ Dronedaronone also significantly reduced cardiovascular mortality, specifically arrhythmic death
- ▶ Dronedaronone 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 dronedaronone were achieved without serious safety concerns with a low risk for pro-arrhythmia and no organ toxicity

The landmark ATHENA trial is the largest morbidity-mortality study with an AAD ever conducted in AF patients

Dronedaronone 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

Dronedaronone also significantly reduced cardiovascular mortality, specifically arrhythmic death

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For AF-related as well as non-AF-related reasons

The unique CV outcomes observed in ATHENA with dronedaronone were achieved without serious safety concerns with a low risk for pro-arrhythmia and no organ toxicity

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