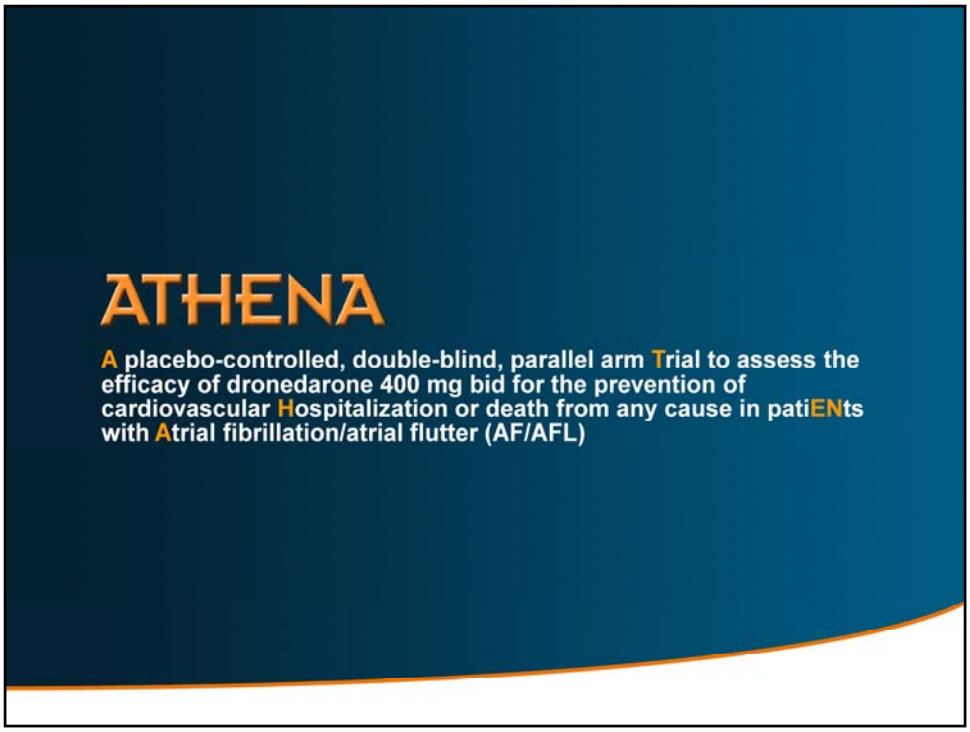
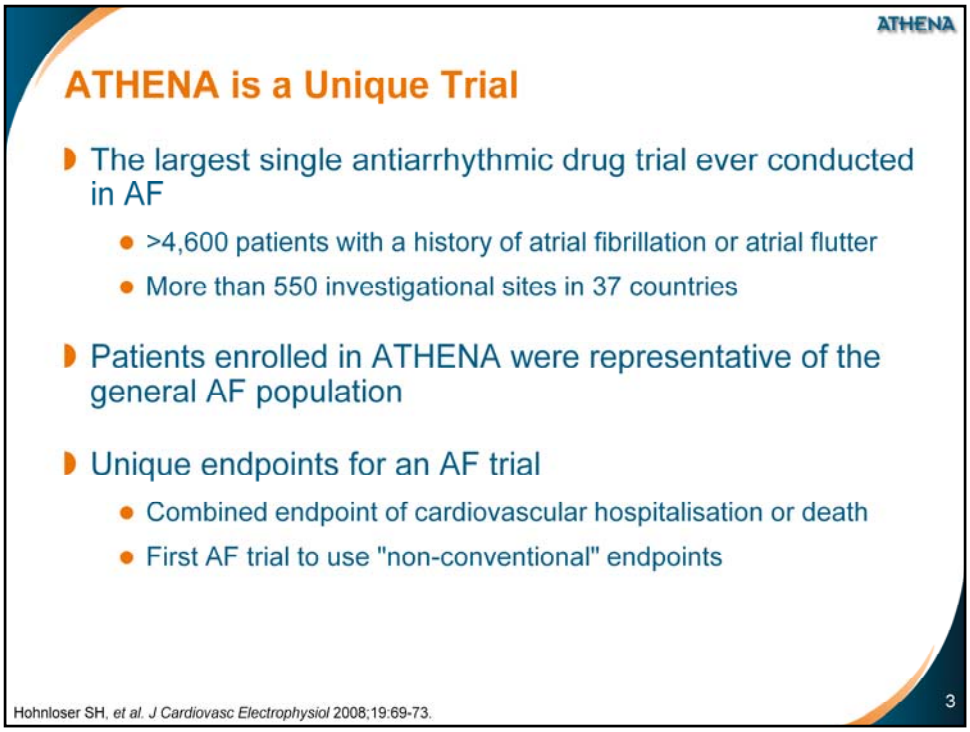
ATHENA

- 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



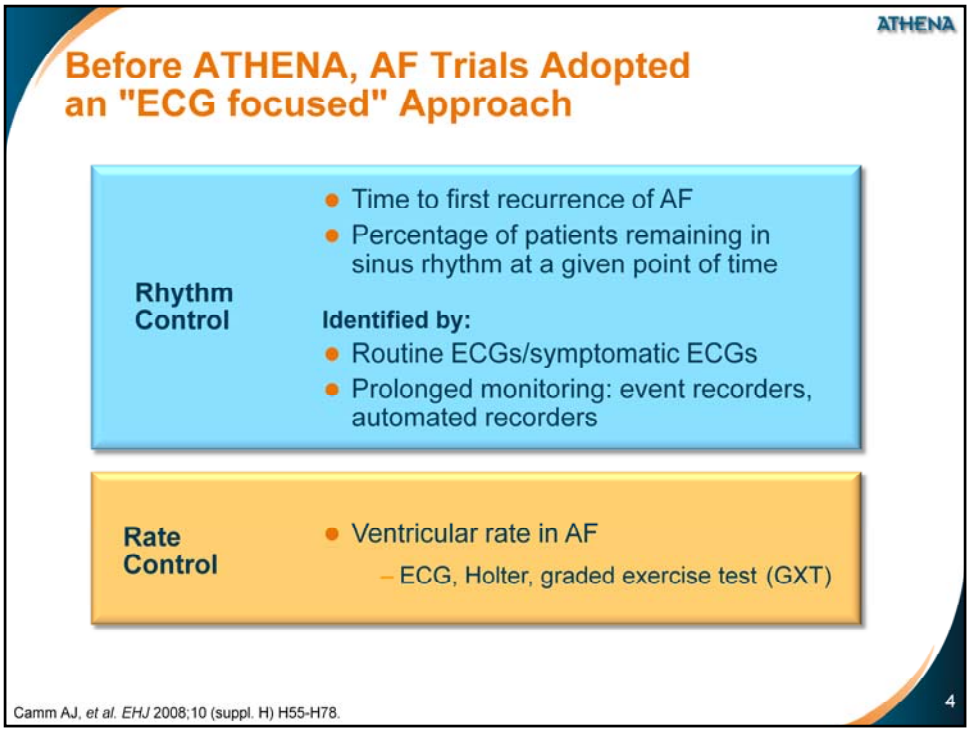
ATHENA is a unique trial in several ways:

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

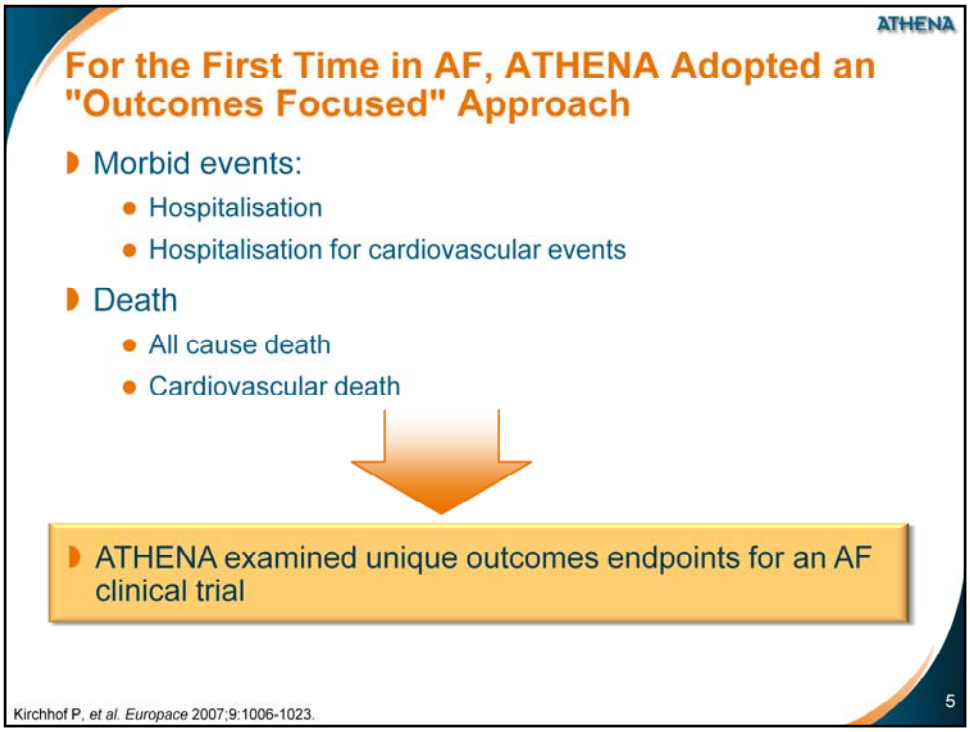
Reference

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



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

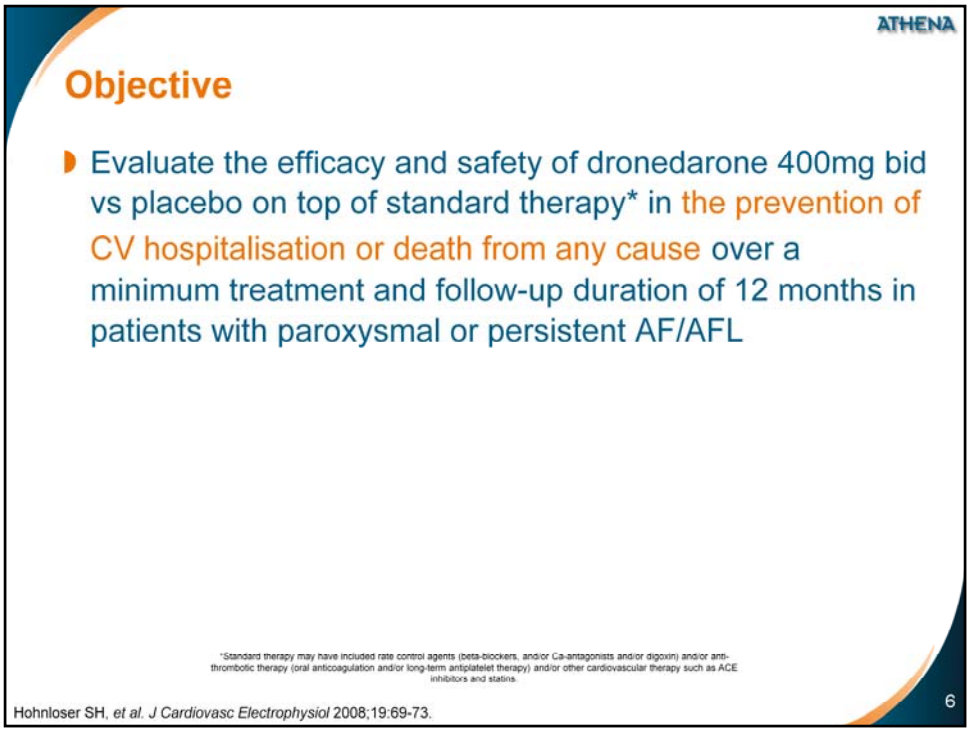
Reference
Camm AJ et al., EHJ 2008; 10 (suppl. H) H55-H78



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



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.

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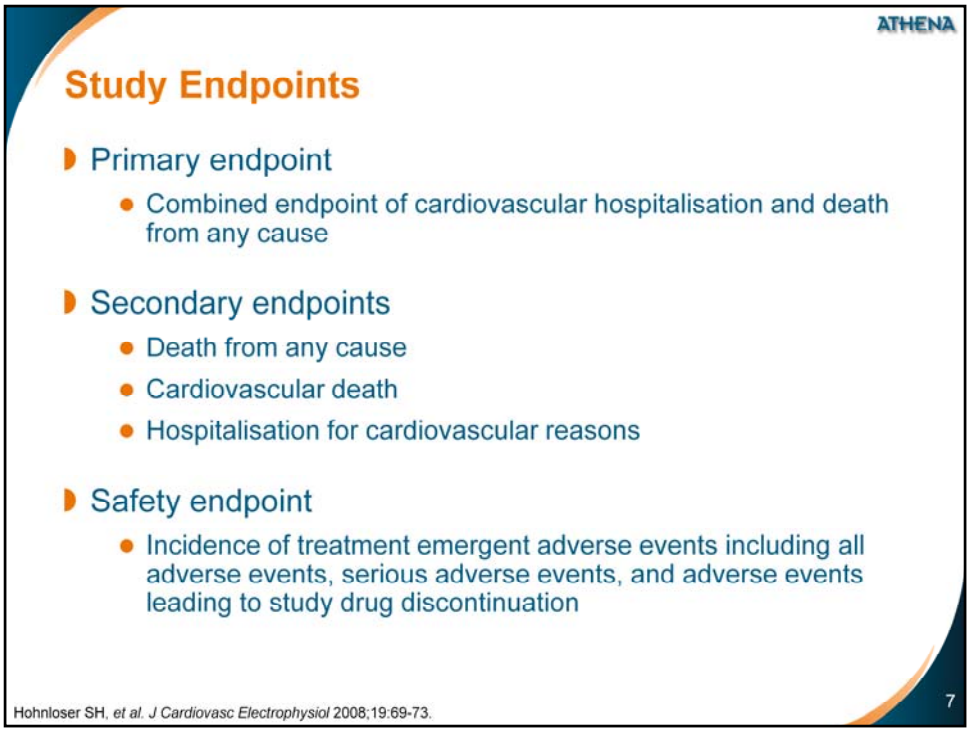
Hohnloser SH et al. J Cardiovasc Electrophysiol 2008;19:69-73.

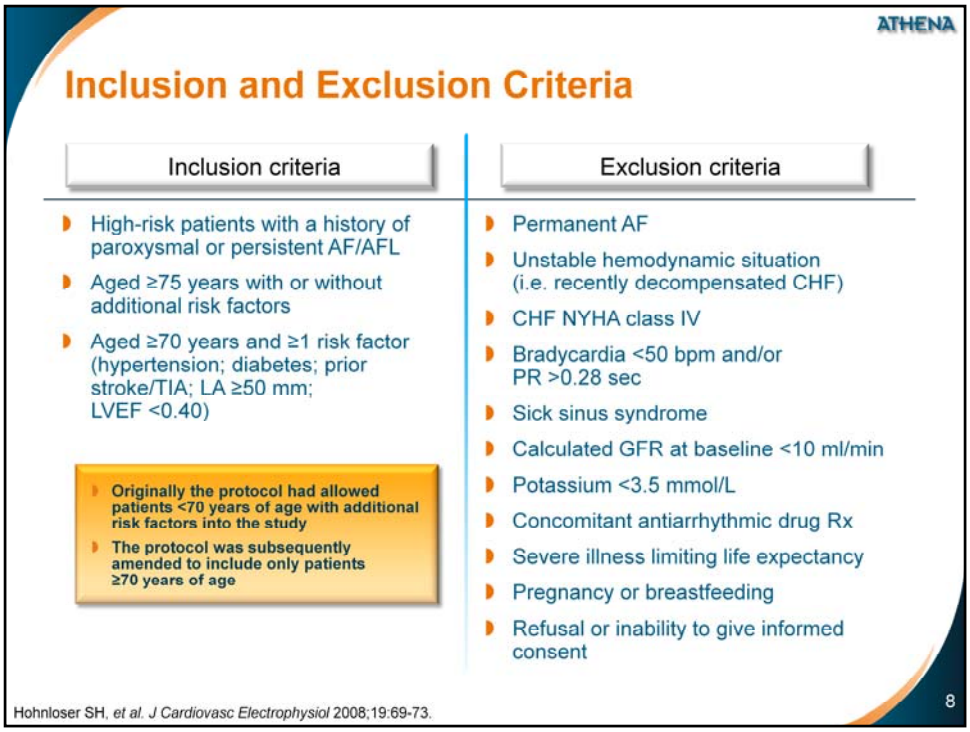


The primary composite endpoint was cardiovascular hospitalisation and all-cause mortality

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

Reference

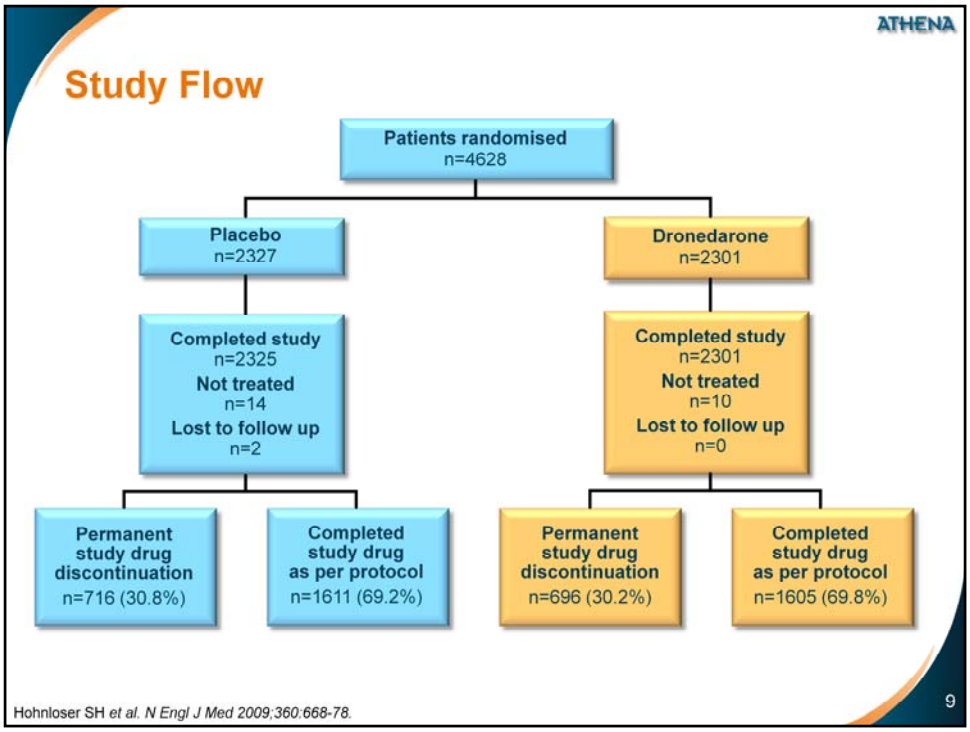
Hohnloser SH et al. J Cardiovasc Electrophysiol 2008;19:69-73.



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

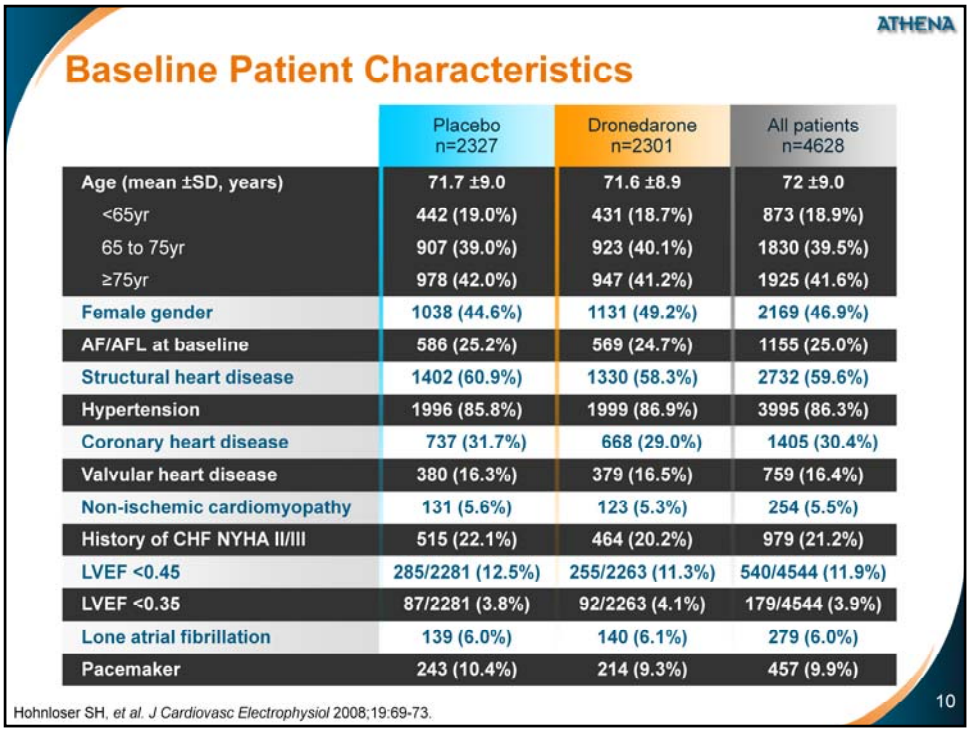
Hohnloser SH et al. J Cardiovasc Electrophysiol 2008;19:69-73.



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.



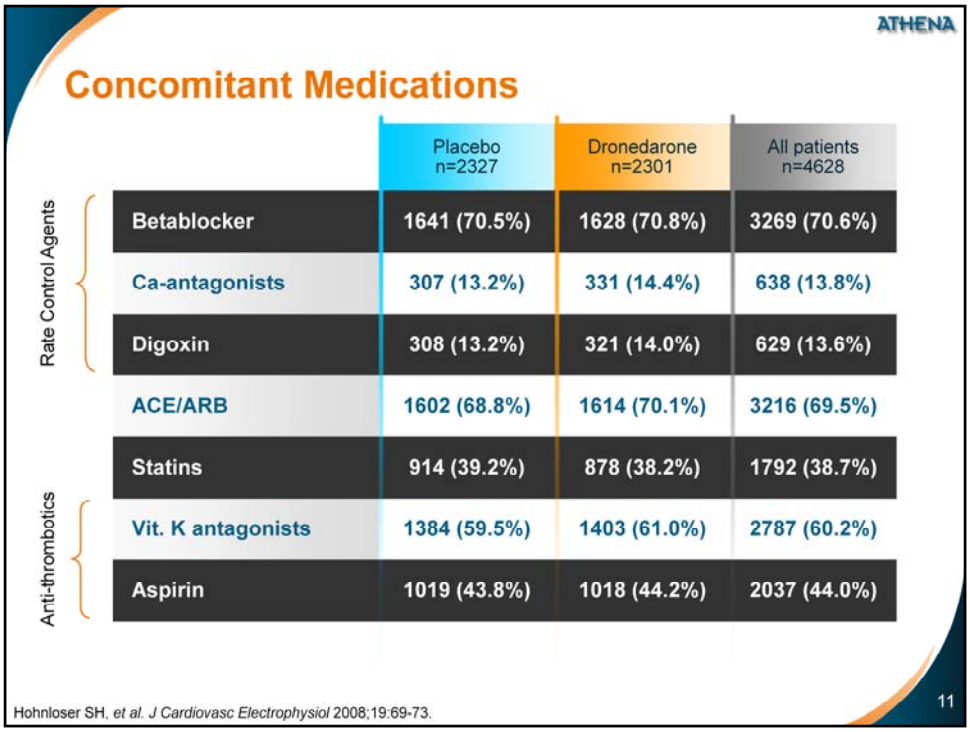
Among the patients included in ATHENA,

- 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.

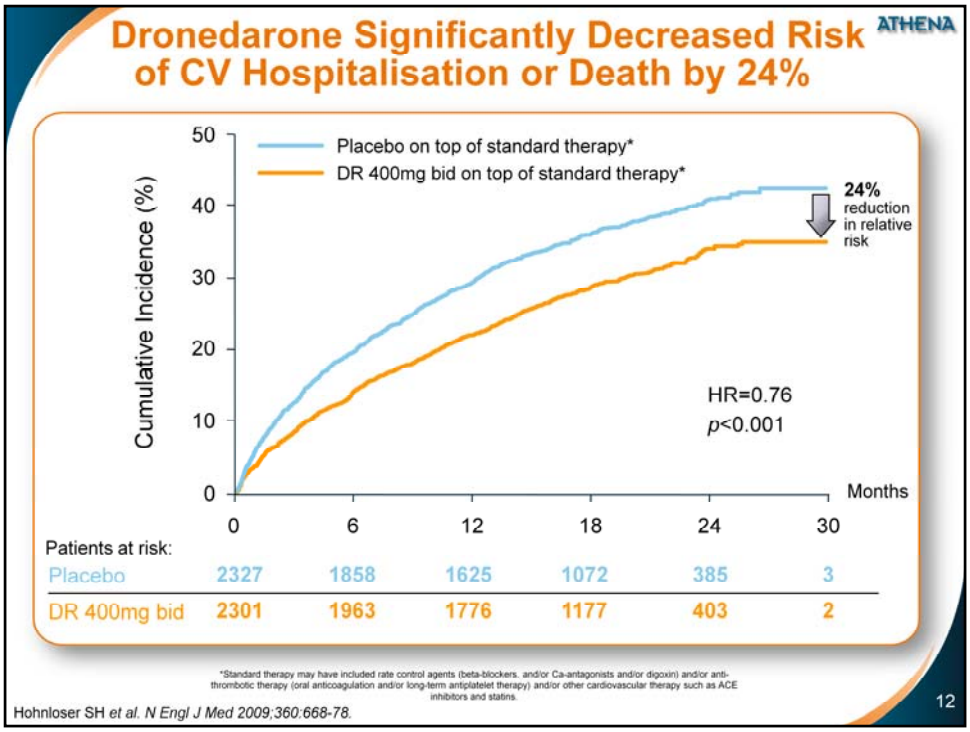


The benefit of dronedarone was obtained on top of standard background therapy, which may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and /or aspirin and other antiplatelets therapy) and/or other cardiovascular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

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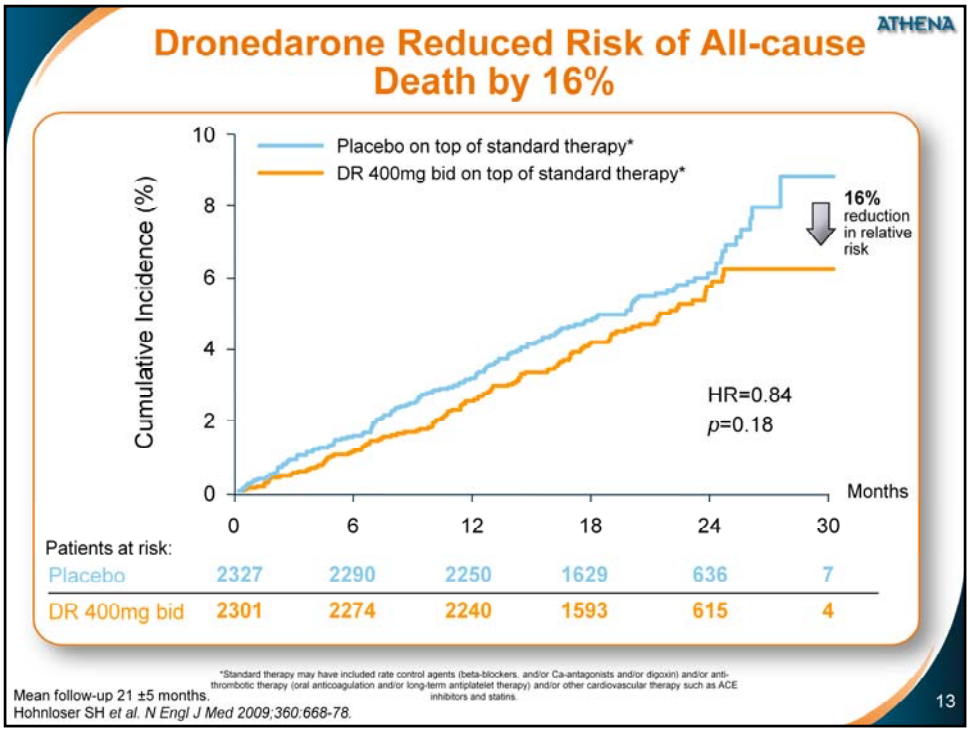
Hohnloser SH et al. N Engl J Med 2009;360:668-78.



There were numerically fewer deaths (relative risk reduction of 16%) from any cause in the Dronedarone 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

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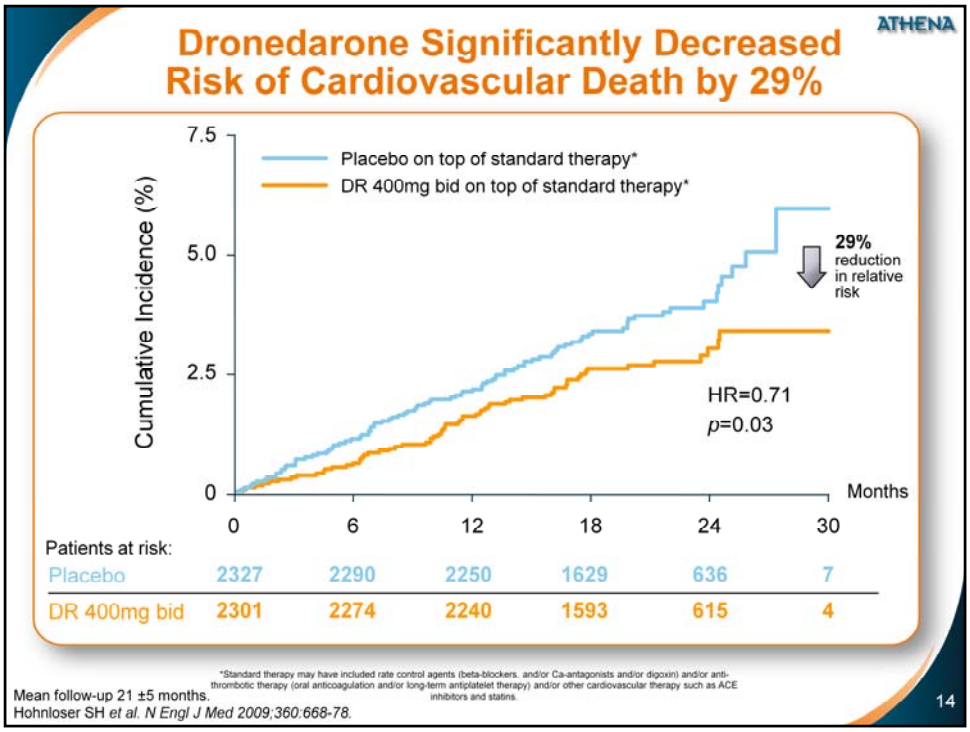

Dronedarone significantly decreased the risk of cardiovascular death by 29% (p=0.03) on top of standard therapy, including rate control and antithrombotic drugs

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

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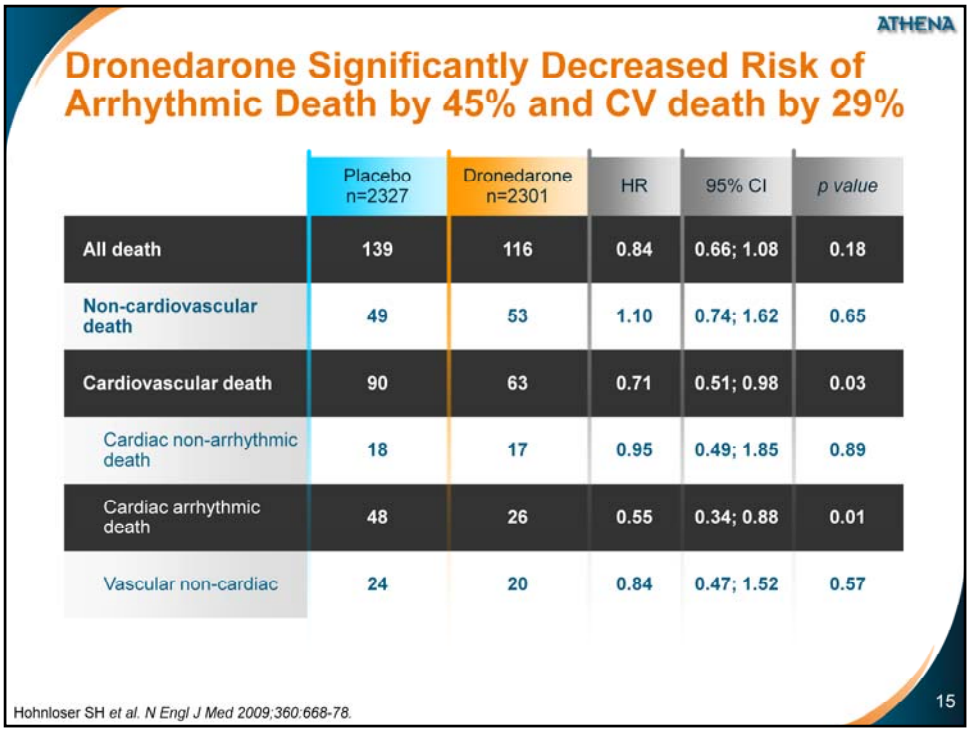
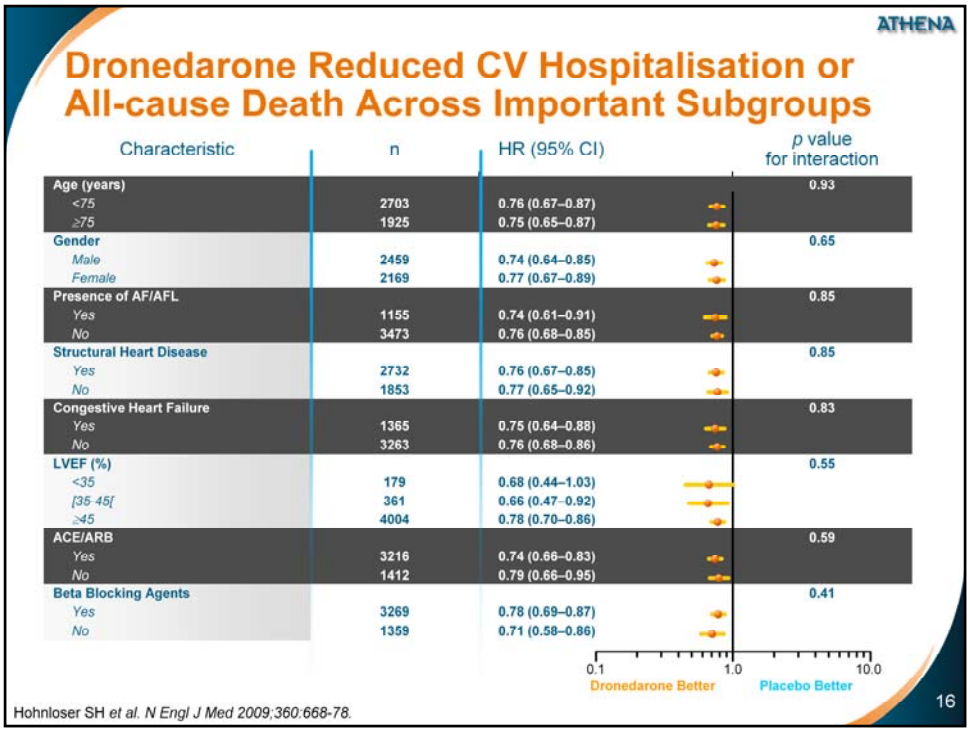


Along with the significant decrease in cardiovascular death (29%;p=0.03), Dronedarone also significantly decreased the risk for arrhythmic death, or sudden death, by 45% (p=0.01)

Reference

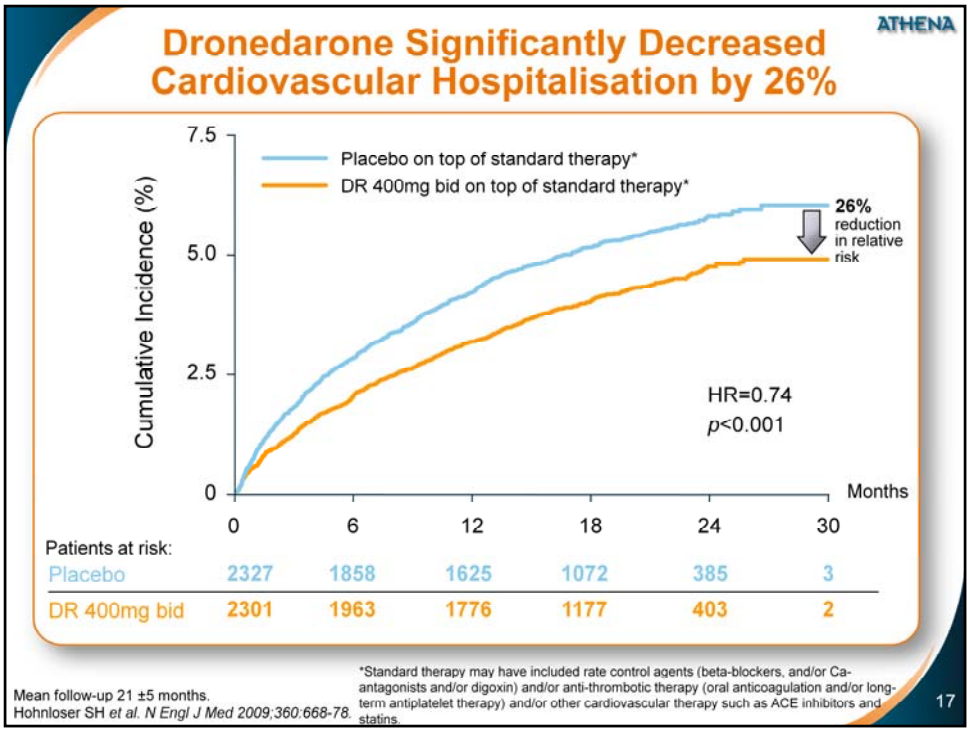
Hohnloser SH et al. N Engl J Med 2009;360:668-78.



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

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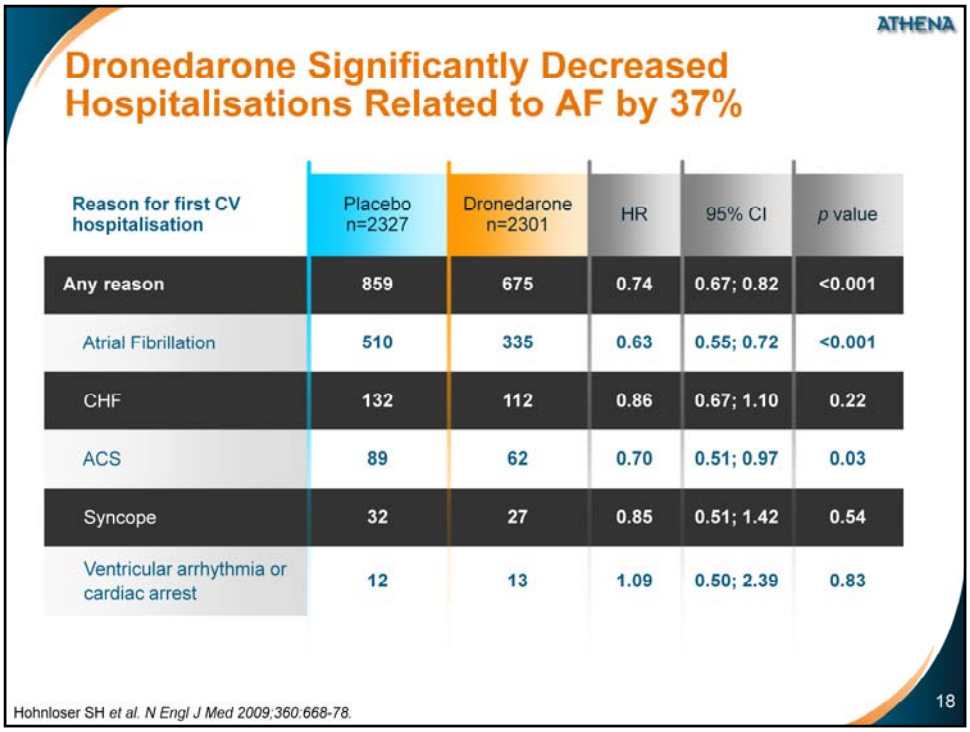
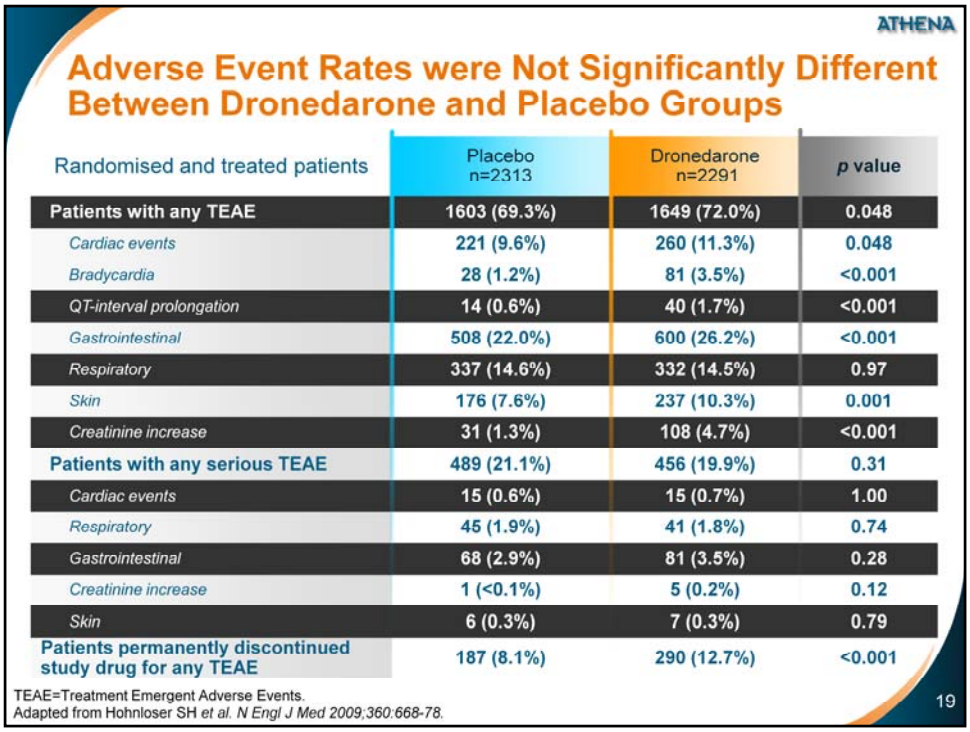


Dronedarone reduced the incidence of all CV-related first hospitalisation by 26% (p<0.001)

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.

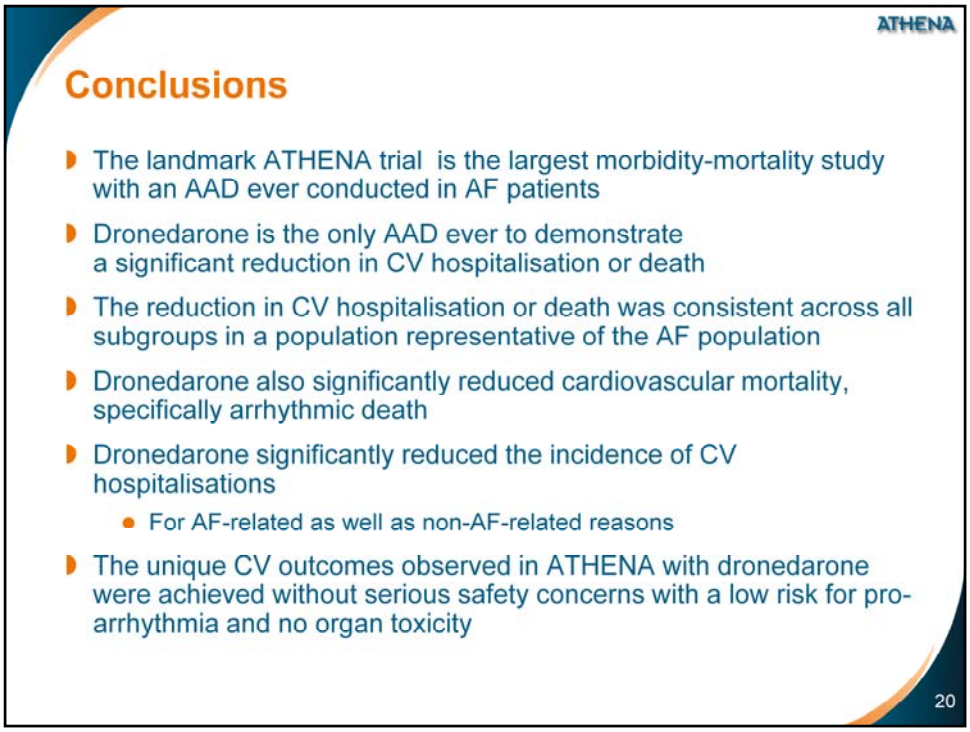


The most common adverse events in the dronedarone arm were:

- 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 creatine 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.



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

Reference

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