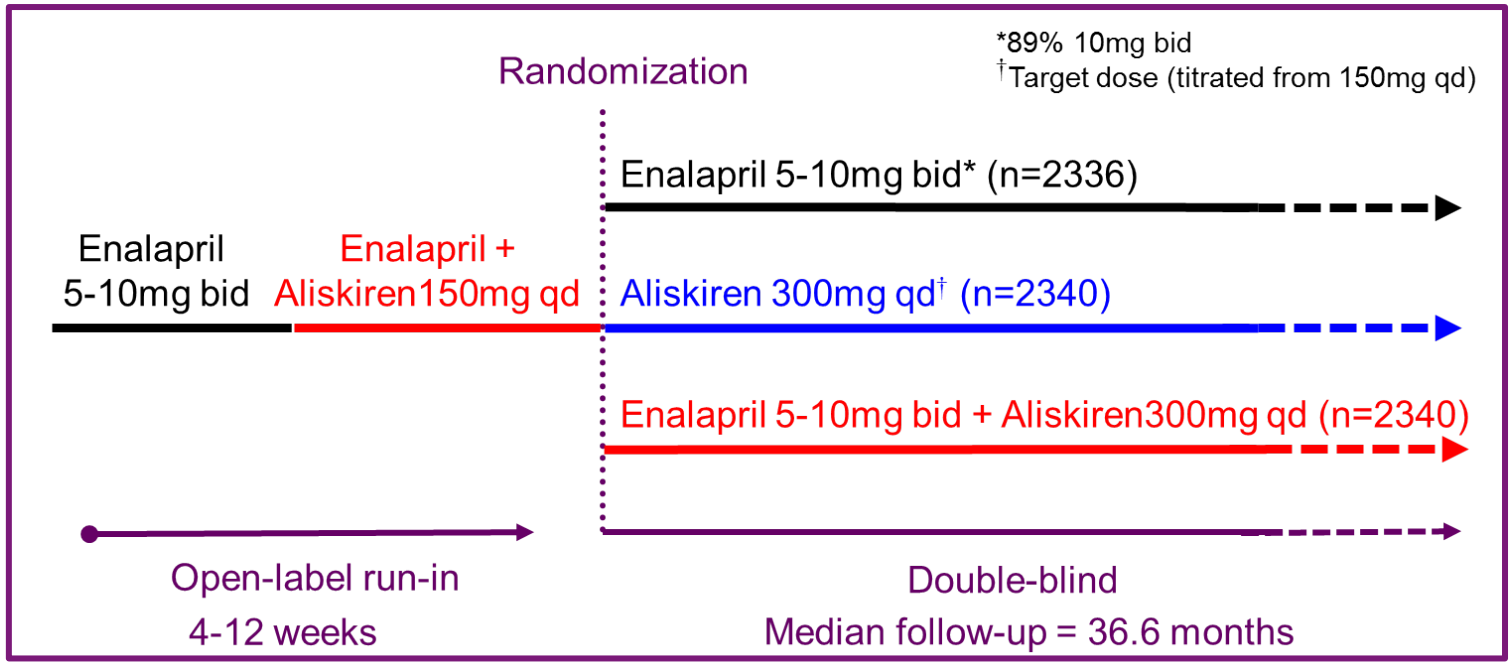
Background: Renin inhibition in heart failure with reduced ejection fraction (HF-REF)

- ACE inhibitors reduce mortality and reduce heart failure hospitalization rates in patients with HF-REF, across the spectrum of symptom severity (CONSENSUS, SOLVD).
- ARBs are an *alternative* in patients unable to tolerate an ACE inibitor because of cough (CHARM-Alternative).
- ARBs futher reduce cardiovascular mortality (CHARM-Added) and heart failure hospitalization (CHARM-Added, Val-HeFT) when *added to* an ACE inhibitor.
- Might a direct renin inhibitor (aliskiren) add to the benefit of an ACE inhibitor or be a better alternative to an ACE inhibitor?

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE)

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.35
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background ACEi therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker unless contraindicated/not tolerated
- SBP ≥95 mmHg run-in/ ≥90 mmHg at randomization
- eGFR ≥35 ml/min/1.73m^2 at randomization /no decrease >25% during run in
- Potassium <5.0 mmol/l run-in/ <5.2 mmol/l at randomization



ATMOSPHERE: Baseline characteristics

	Aliskiren+Enalapril (n=2340)	Aliskiren (n=2340)	Enalapril (n=2336)
Age (years)	63.2 ± 11.7	63.3 ± 12.1	63.3 ± 11.7
Women (%)	21.1%	22.7%	21.4%
Ischemic etiology (%)	57.1%	55.3%	55.7%
LVEF (%)	28.5 ± 5.7	28.4 ± 5.7	28.3 ± 5.7
NYHA class II / III (%)	64.0% / 33.7%	64.0% / 34.3%	61.7% / 36.3%
Systolic BP (mm Hg)	124 ± 19	124 ± 18	123 ± 18
Heart rate (beats/min)	72 ± 13	72 ± 12	72 ± 13
NT pro-BNP (pg/ml)	1193 (640-2351)	1167 (627-2173)	1223 (634-2194)
History of diabetes	28.4%	26.8%	27.9%
Digitalis	32.7%	32.0%	31.2%
Beta-blocker	92.0%	91.2%	91.9%
MRA	36.6%	36.9%	37.8%
CRT-P/CRT-D	6.1%	5.1%	5.6%
ICD/CRT-D	15.0%	15.5%	14.4%

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE)

In reducing the risk of the primary composite outcome of cardiovascular death or heart failure hospitalization

Superiority hypotheses

- **Aliskiren added to enalapril** is superior to enalapril
- **Aliskiren monotherapy** is superior to enalapril

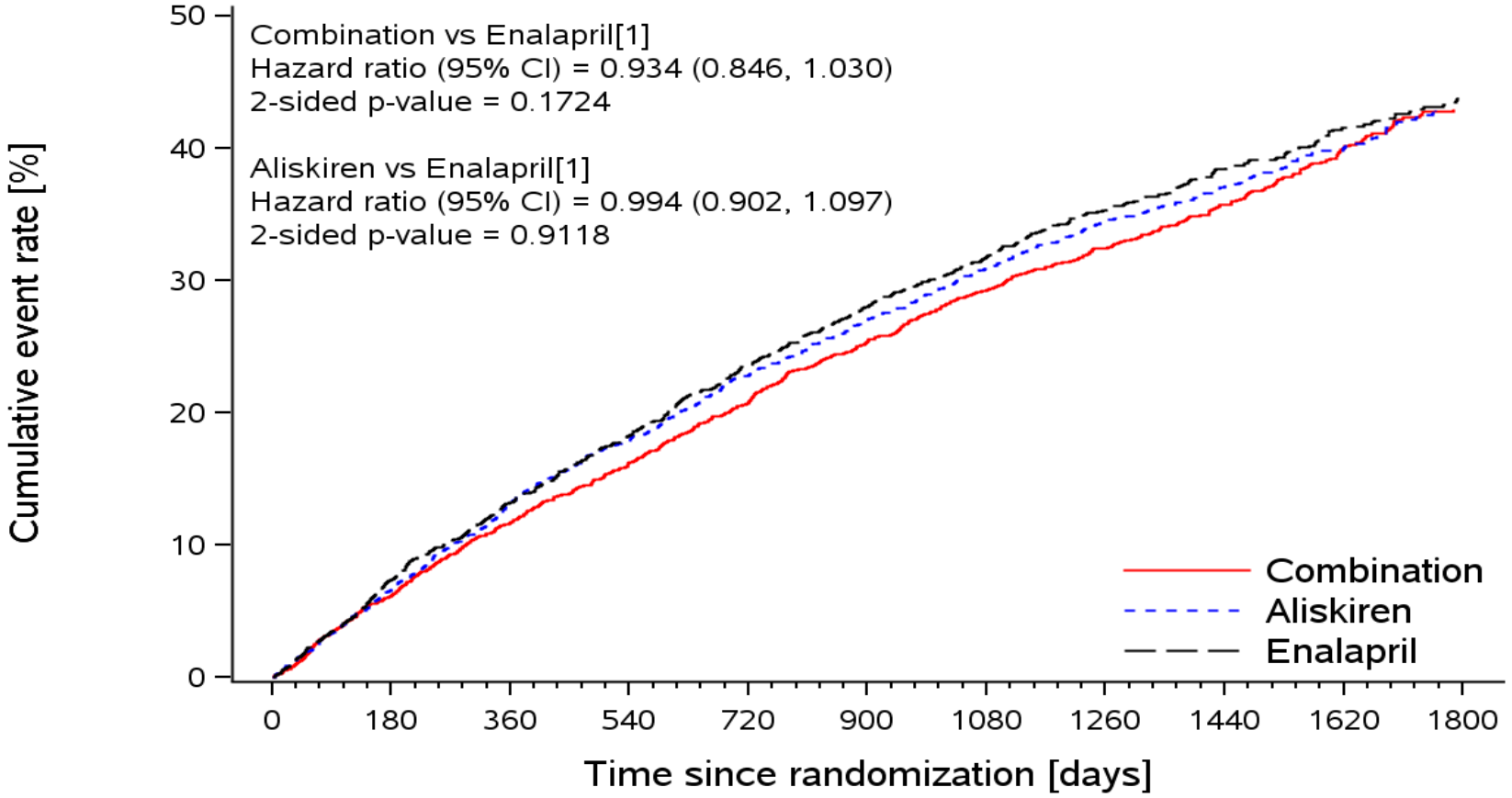
Non-inferiority hypothesis

- **Aliskiren monotherapy** is non-inferior to enalapril

https://clinicaltrials.gov NCT00853658

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

ATMOSPHERE: Primary outcome



Patients at risk

Combination	2340	2137	1959	1809	1562	1307	1085	895	689	456	273
Aliskiren	2340	2127	1934	1761	1510	1288	1064	888	681	474	282
Enalapril	2336	2128	1947	1766	1513	1268	1044	866	679	452	281

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

ATMOSPHERE: Comparison of enalapril and aliskiren monotherapy (non-inferiority)

Pre-specified criterion for declaring non-inferiority was a P-value ≤0.0123 (one-sided)

	Aliskiren (n=2340)	Enalapril (n=2336)	HR (95% CI)	P value
All patients n (%)	791 (33.8%)	808 (34.6%)	0.99 (0.90-1.10)	0.0184*

***Did not meet the pre-specified P-value for significance**

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

ATMOSPHERE: Secondary and exploratory outcomes

Secondary outcome:

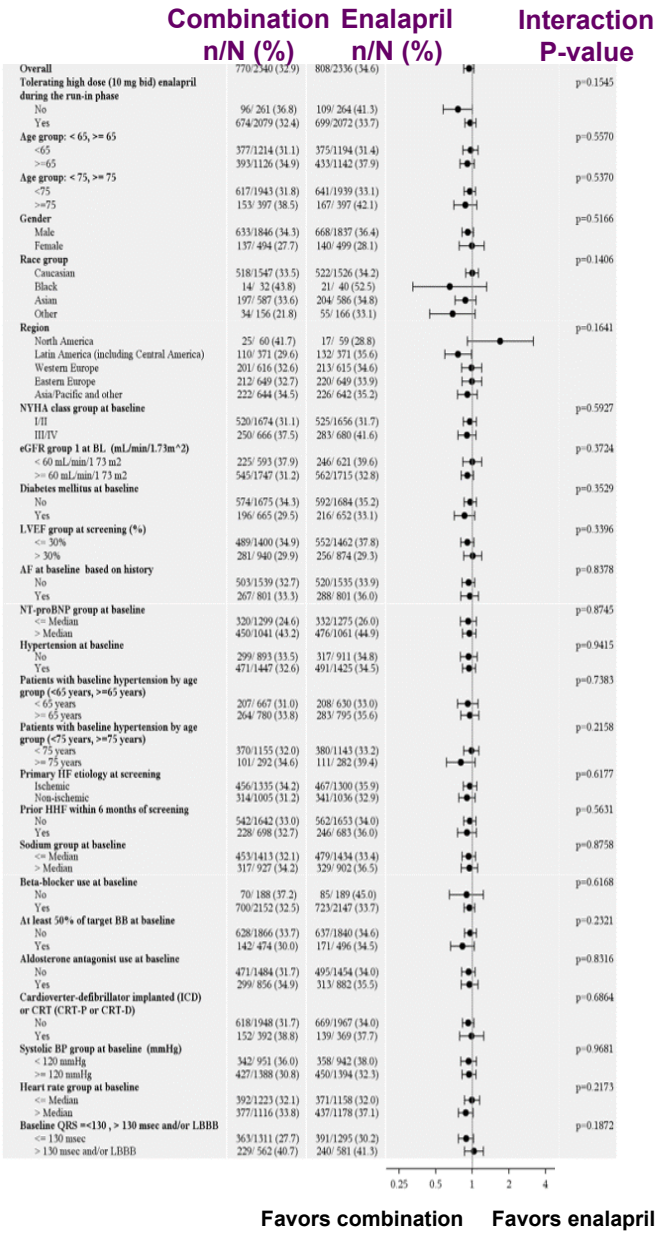
- Kansas City Cardiomyopathy Questionnaire (KCCQ) - Change in the clinical summary score (CSS) from baseline to 12 months

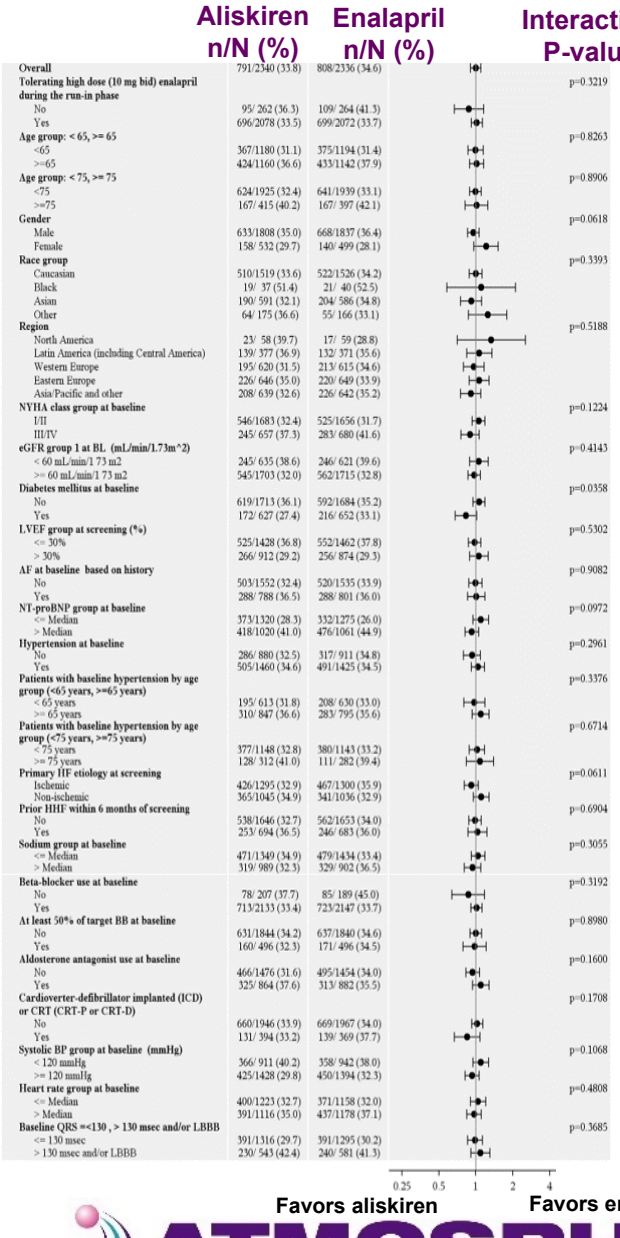
Exploratory outcomes (selected):

- Composite CV outcome: CV death, HF hospitalization, MI, stroke or resuscitated cardiac arrest
- Composite renal outcome: renal death, ESRD (initiation of dialysis, renal transplantation, or a serum Cr above 6.0 mg/dl [530 µmol/l]), or doubling of serum Cr from baseline (to >upper limit of normal) sustained for at least 1 month

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

ATMOSPHERE: Pre-specified subgroups





ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

ATMOSPHERE: Safety outcomes

	Aliskiren+ Enalapril (n=2340)	Aliskiren (n=2340)	Enalapril (n=2336)	P value (1)	P value (2)
Hypotension n (%) Symptoms Symptoms and SBP <90mmHg	 322 (13.8%) 87 (3.7%)	 249 (10.6%) 31 (1.3%)	 258 (11.0%) 55 (2.4%)	 0.005 0.008	 0.67 0.009
Renal impairment n (%) Cr ≥2.5mg/dl Cr ≥3.0mg/dl	 95 (4.1%) 46 (2.0%)	 63 (2.7%) 35 (1.5%)	 62 (2.7%) 29 (1.2%)	 0.009 0.06	 1.00 0.53
Hyperkalemia n (%) K^+ >5.5mmol/l K^+ >6.0mmol/l	 401 (17.1%) 116 (5.0%)	 255 (10.9%) 70 (3.0%)	 291 (12.5%) 83 (3.6%)	 <0.0001 0.02	 0.10 0.29
Cough n (%)	290 (12.4%)	241 (10.3%)	284 (12.2%)	0.83	<0.05

(1) = Comparison of enalapril plus aliskiren versus enalapril; (2)= Comparison of aliskiren versus enalapril

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE

Summary and conclusions

Combination therapy

- The addition of aliskiren to an evidence-based dose of enalapril led to more adverse events without an increase in benefit.
- This finding differs from the prior ARB “add-on” trials and may reflect a difference in study design (the previous trials did not require an evidence-based dose of background ACE inhibitor).
- There is probably a ceiling to RAS blockade in heart failure, above which there is no further benefit

Aliskiren monotherapy

- Non-inferiority was not demonstrated for aliskiren compared with enalapril.

ATMOSPHERE
Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE