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ORIGINAL ARTICLE

Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure

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ABSTRACT

BACKGROUND

Among patients with chronic heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and hospitalization, but the role of a renin inhibitor in such patients is unknown. We compared the ACE inhibitor enalapril with the renin inhibitor aliskiren (to test superiority or at least noninferiority) and with the combination of the two treatments (to test superiority) in patients with heart failure and a reduced ejection fraction.

METHODS

After a single-blind run-in period, we assigned patients, in a double-blind fashion, to one of three groups: 2336 patients were assigned to receive enalapril at a dose of 5 or 10 mg twice daily, 2340 to receive aliskiren at a dose of 300 mg once daily, and 2340 to receive both treatments (combination therapy). The primary composite outcome was death from cardiovascular causes or hospitalization for heart failure.

RESULTS

After a median follow-up of 36.6 months, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group and in 808 (34.6%) in the enalapril group (hazard ratio, 0.93; 95% confidence interval [CI], 0.85 to 1.03). The primary outcome occurred in 791 patients (33.8%) in the aliskiren group (hazard ratio vs. enalapril, 0.99; 95% CI, 0.90 to 1.10); the prespecified test for noninferiority was not met. There was a higher risk of hypotensive symptoms in the combination-therapy group than in the enalapril group (13.8% vs. 11.0%, P=0.005), as well as higher risks of an elevated serum creatinine level (4.1% vs. 2.7%, P=0.009) and an elevated potassium level (17.1% vs. 12.5%, P<0.001).

CONCLUSIONS

In patients with chronic heart failure, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit. Noninferiority was not shown for aliskiren as compared with enalapril. (Funded by Novartis; ATMOSPHERE ClinicalTrials.gov number, NCT00853658.)

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*Deceased.

†A list of participating centers and investigators in the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) is provided in the Supplementary Appendix, available at NEJM.org.

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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

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ATMOSPHERE: Censoring of patients with diabetes*

- Following the results of ALTITUDE (aliskiren added to an ACEi/ARB in patients with diabetes and CKD/CVD) and ASTRONAUT (aliskiren added to an ACEi/ARB in patients hospitalized with HF), the Clinical Trials Facilitation Group of the Heads of Medicines Agencies in Europe requested that patients with diabetes have study drug discontinued.
- Follow-up *for the efficacy analyses* in patients with diabetes (and some others) who had treatment discontinued because of a regulatory request was censored at the date of implementation of these requests. Patients off study drug were still followed to end of the trial.
- Median follow-up for analysis of efficacy in patients with diabetes was 24.1 months, and in patients without diabetes was 46.0 months.

*and some others

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ATMOSPHERE: Entry criteria

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.35
- BNP ≥150 pg/mL (NT-proBNP ≥600 pg/mL) or if HF hosp. within 12 mo. BNP ≥100 pg/mL (NT-proBNP ≥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

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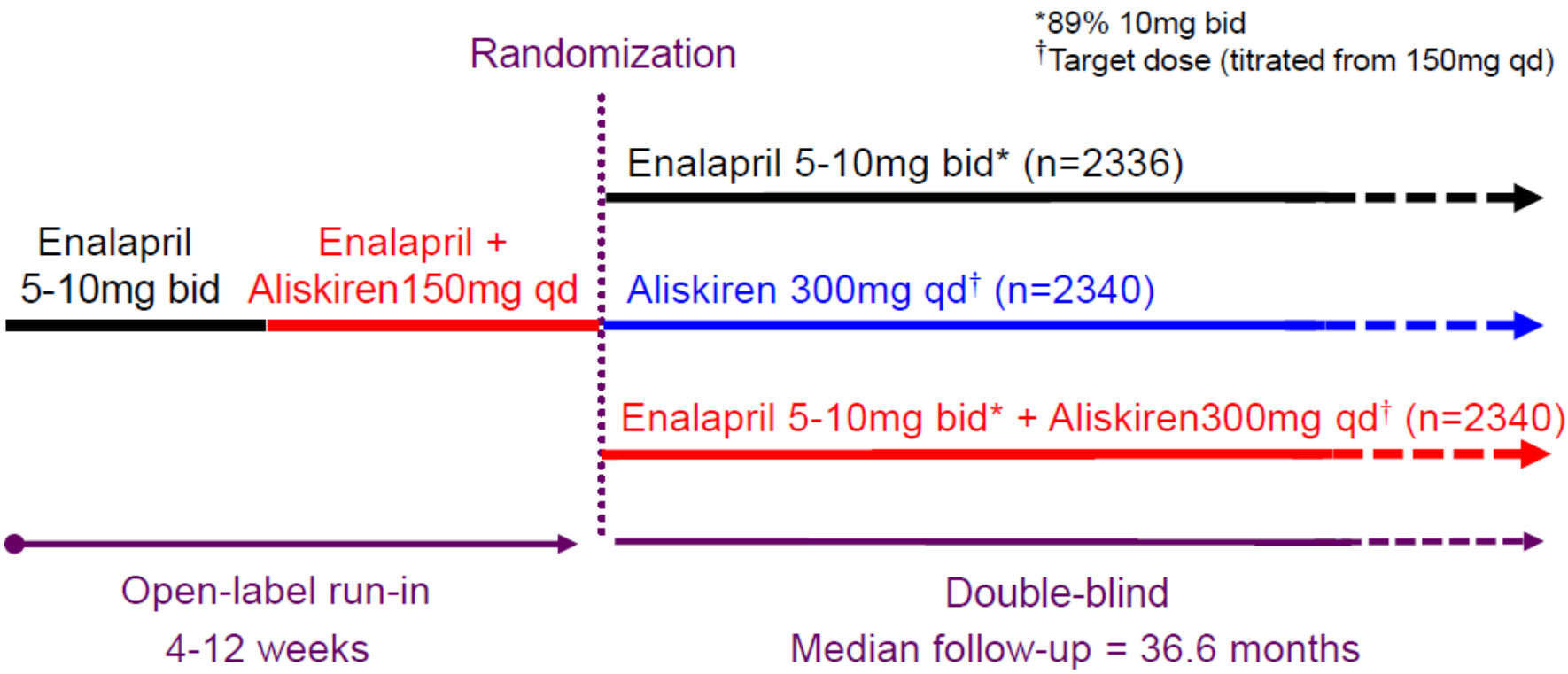
ATMOSPHERE: Trial design

Primary outcome: CV death or heart failure hospitalization

(event driven: target 2318 patients [2369 accrued])



Prior ACEi use discontinued

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ATMOSPHERE is one of the largest HF trials

- Number of Patients screened: 14,306
- Number of case report forms completed & signed-off by Investigators: 1.7 million +
- Number of SAEs reported: 15,800+
- Number of AEs reported: 58,000+
- Number of lab records: 1,787,000+
- Number of data queries raised: 1.2 million +
- Number of terms coded (adverse events & concomitant medications): 324,000+
- Number of clinical endpoints adjudicated by CEC: 8800+

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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
BMI	27.3 ± 5.3	27.4 ± 5.4	27.3 ± 5.3
NT-proBNP (pg/mL)	1193 (640-2351)	1167 (627-2173)	1223 (634-2194)
Baseline eGFR ($mL/min/1.73\ m^2$)	74.1 ± 27	74.0 ± 23	73.9 ± 22

* At screening

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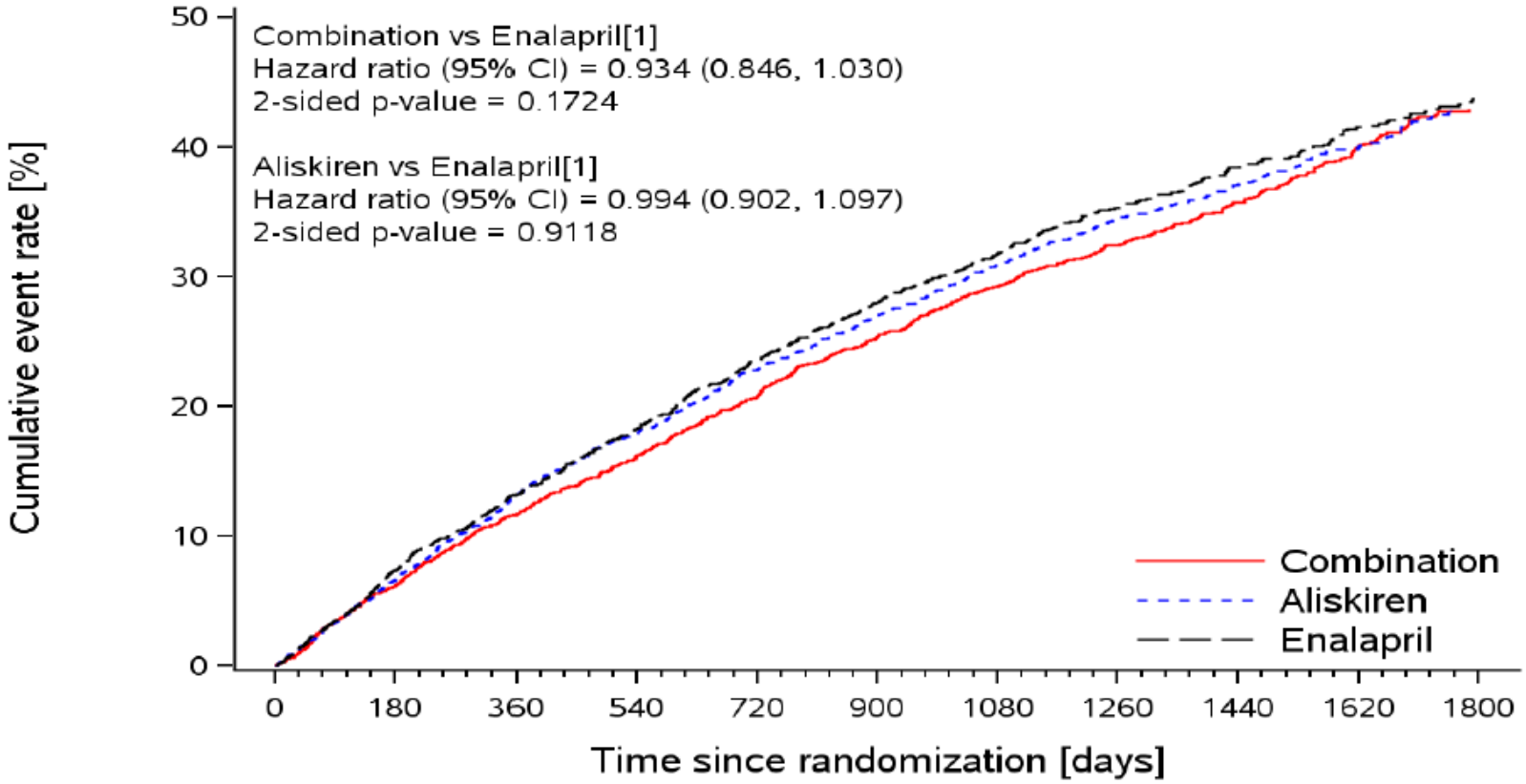
ATMOSPHERE: Primary outcome



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

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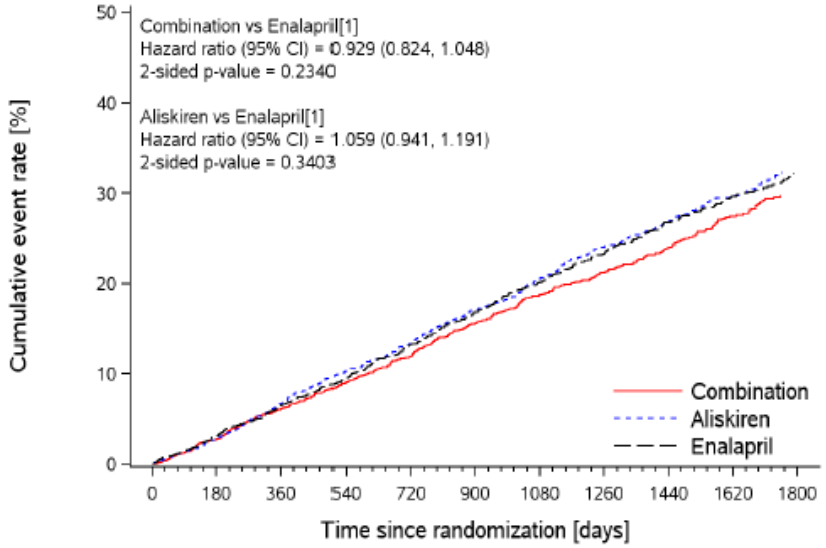
ATMOSPHERE: Components of the primary composite outcome

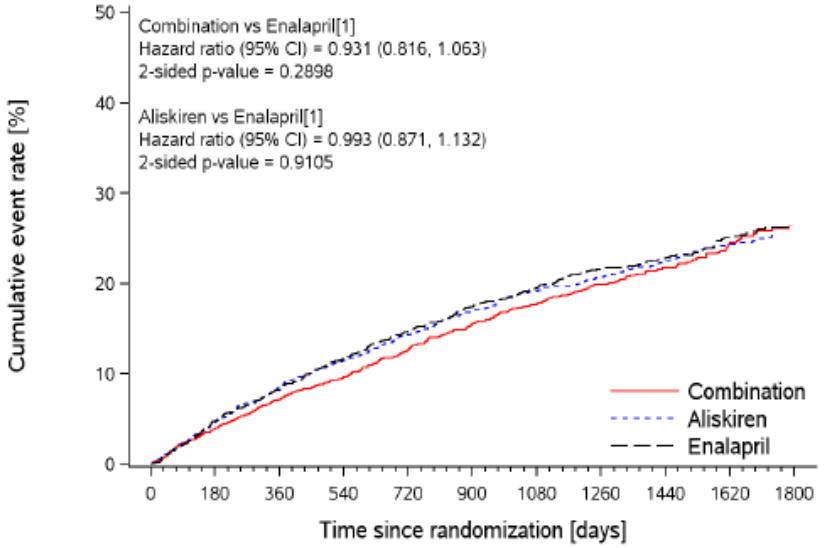
CV death



Patients at risk

Combination	2340	2214	2080	1956	1725	1468	1235	1032	805	548	335
Aliskiren	2340	2214	2073	1918	1690	1454	1211	1015	788	564	338
Enalapril	2336	2222	2093	1950	1711	1454	1208	1010	794	539	336

HF hospitalization



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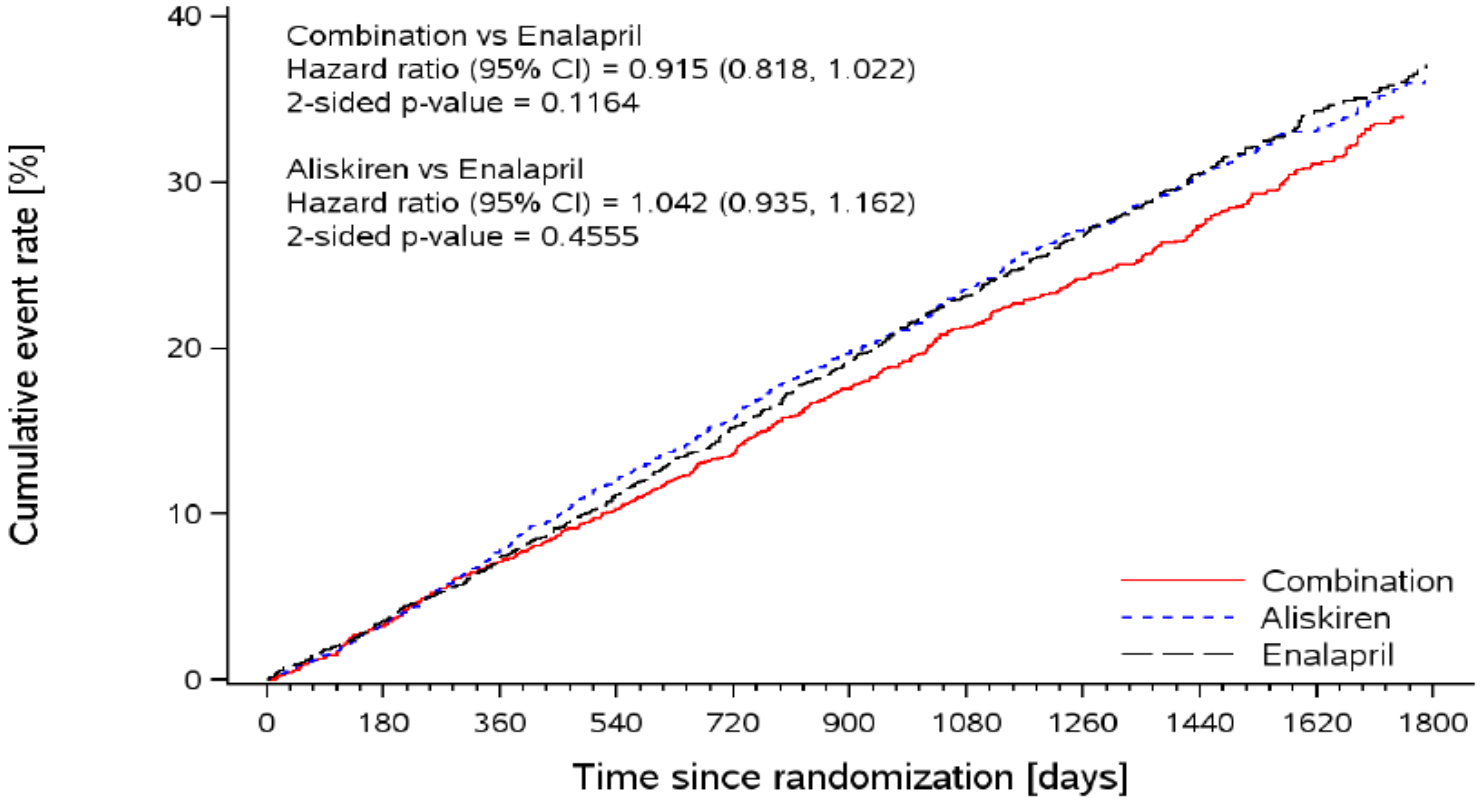
ATMOSPHERE: All-cause mortality



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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.

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