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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ANGIOTENSIN-CONVERTING–ENZYME (ACE) inhibitors are effective in lowering the risks of death and hospitalization among patients with chronic heart failure and reduced ejection fraction.[1,2] As a consequence, there has been interest in other approaches to interruption of the renin–angiotensin system in patients with heart failure. Angiotensin-receptor blockers (ARBs) were the first alternative tested, and in one placebo-controlled trial, candesartan was associated with lower risks of death from cardiovascular causes and hospitalization for heart failure among patients who could not take ACE inhibitors.[3] However, in a head-to-head comparison, losartan was not as effective as captopril.[4]

The combination of an ARB and an ACE inhibitor has also been examined in two trials involving patients with heart failure.[5,6] In both trials, the addition of an ARB to standard therapy with an ACE inhibitor was associated with a lower risk of hospitalization for heart failure than was standard therapy alone and, in one trial, with a lower risk of death from cardiovascular causes. Neither trial, however, mandated an evidence-based dose of ACE inhibitor, and subsequent trials that did so showed that the addition of an ARB was ineffective in patients with myocardial infarction and in other patients at high cardiovascular risk.[7,8]

Renin inhibition offers another approach to interruption of the renin–angiotensin system.[9-11] We tested whether combining the renin inhibitor aliskiren with the ACE inhibitor enalapril was superior to enalapril alone and whether aliskiren was at least noninferior to enalapril in patients with heart failure.[12,13]

METHODS

TRIAL OVERSIGHT

The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) was a randomized trial comparing enalapril alone with aliskiren alone and with the combination of aliskiren and enalapril in patients with heart failure. The design of the trial and the characteristics of the patients at baseline have been published previously.[12,13] The executive committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed and oversaw the conduct of the trial in collabo-

ration with the sponsor (Novartis). The trial protocol, which is available at NEJM.org, was approved by the ethics committee at each center. Data were collected and analyzed by the sponsor according to a prespecified statistical analysis plan; the analyses were replicated by an independent statistician, who is one of the authors. The initial draft of the manuscript was prepared by the first author and edited by all the authors, who had unrestricted access to the data and agreed to submit the manuscript for publication. The authors assume responsibility for the accuracy and completeness of the data and analyses as well as for the fidelity of this report to the trial protocol.

PATIENTS

Eligible patients had chronic heart failure with New York Heart Association (NYHA) class II to IV symptoms and an ejection fraction of 35% or less. Participants were also required to have a plasma B-type natriuretic peptide (BNP) concentration of 150 pg or more per milliliter (or an N-terminal pro-BNP [NT-proBNP] concentration of ≥600 pg per milliliter) or, if they had been hospitalized for heart failure within the previous 12 months, a BNP concentration of 100 pg or more per milliliter (or an NT-proBNP concentration of ≥400 pg per milliliter). Participants must have been receiving stable doses of an ACE inhibitor (equivalent to at least 10 mg of enalapril daily) and of a beta-blocker at the time of enrollment.

Exclusion criteria included symptomatic hypotension, a systolic blood pressure of less than 95 mm Hg at screening (or <90 mm Hg at randomization), an estimated glomerular filtration rate (GFR) of less than 40 ml per minute per 1.73 m² of body-surface area at screening (or <35 ml per minute per 1.73 m² at randomization or a decline of >25% in the estimated GFR between screening and randomization), a serum potassium concentration of 5.0 mmol or more per liter at screening (or ≥5.2 mmol per liter at randomization), and a history of inability to take ACE inhibitors. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

PROCEDURES

The trial included a two-part run-in phase. After switching from their existing ACE inhibitor, eligible patients entered the first part of the run-

in phase, during which they received 1 to 4 weeks of enalapril at a dose of 5 mg twice daily, in a single-blind fashion, followed (if the level of adverse events was not unacceptable) by 2 to 4 weeks of enalapril at a dose of 10 mg twice daily; patients who had been taking a dose of ACE inhibitor that was equivalent to 20 mg of enalapril daily before the trial could start at the second step directly. At the end of this period, patients were stratified according to the dose of enalapril that could be taken without unacceptable adverse events: 5 mg twice daily (low-dose stratum) or 10 mg twice daily (high-dose stratum). Patients then entered the second part of the run-in phase, during which they received aliskiren at a dose of 150 mg once daily, in a single-blind fashion, in addition to enalapril.

Patients who could take both treatments were randomly assigned, in a 1:1:1 ratio, to double-blind, double-dummy treatment in one of three groups with the use of a voice-based computerized randomization system involving concealed trial-group assignments. Patients were assigned to the combination of enalapril at a dose of 5 or 10 mg twice daily and aliskiren at a dose of 150 mg once daily, aliskiren at a dose of 150 mg once daily, or enalapril at a dose of 5 or 10 mg twice daily. Two weeks after randomization, the dose of aliskiren was increased to 300 mg once daily in the combination-therapy group and the aliskiren group, with sham adjustment in the enalapril group. Patients were evaluated every 2 to 8 weeks during the first 4 months and every 4 months thereafter. The dose could be decreased in patients who could not take the target doses.

OUTCOMES

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The secondary outcomes were the change from baseline to 12 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score and the change in the NT-proBNP concentration from baseline to 4 months (this outcome was removed after the protocol was amended, as explained below).[12-14] Additional prespecified exploratory outcomes are listed in Table S1 in the Supplementary Appendix. A clinical-event committee adjudicated deaths and major cardiovascular outcomes in a blinded fashion, using prespecified criteria (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The original coprimary objectives were, first, to test whether the combination of aliskiren and enalapril was superior to enalapril for the primary outcome and, second, to test whether aliskiren alone was superior, or at least noninferior, to enalapril with respect to the same outcome. On the basis of our initial power calculation (see the Supplementary Appendix), we estimated that 7041 patients would need to undergo randomization and that 2318 primary-outcome events would need to occur.

While the trial was ongoing, premature termination of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE) because of futility and safety concerns, and the subsequent finding in the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) of worse outcomes in patients with diabetes treated with aliskiren than in those who received placebo, led the Clinical Trial Facilitation Group of the Heads of Medicines Agencies in Europe to mandate that persons with diabetes at baseline and those in whom diabetes developed during the present trial discontinue the treatment and be switched to conventional therapy and that no further patients with diabetes be enrolled. This decision was executed worldwide in a protocol amendment issued in April 2013.[13,15,16]

This decision led to amendment of the statistical analysis plan. In patients with diabetes, follow-up for trial outcomes was censored on the date of the enactment of the protocol amendment (or on the date of other country-specific requests mandating the stopping of the trial treatment). Comparison of the combination therapy with enalapril in patients without diabetes became an additional superiority hypothesis. The change in the NT-proBNP concentration was removed as a secondary outcome.[13] The power for the primary analyses was preserved, as described in the Supplementary Appendix.

Analyses included all the patients who underwent randomization validly, according to the intention-to-treat principle. Time-to-event data were evaluated with the use of Cox proportional-hazards models, as described in the statistical analysis plan (see the protocol). Consistency of treatment effects was assessed among 25 prespecified subgroups by inclusion of an interaction term for each subgroup. The change in the

KCCQ score was evaluated with a repeated-measures analysis. Adverse events were compared with the use of Fisher's exact test; prospectively defined adverse events of interest included hypotension, renal impairment, hyperkalemia, and cough.

All P values are two-sided (except for noninferiority). A gatekeeping procedure that combined hierarchical and simultaneous testing based on Bonferroni adjustment was used to ensure control of the type I error rate for the primary and secondary outcomes (see the Supplementary Appendix). On the basis of this procedure, the prespecified one-sided alpha level for the declaration of noninferiority (for aliskiren vs. enalapril) was 0.0123.

RESULTS

PATIENTS

From March 13, 2009, to December 26, 2013, a total of 8835 patients at 789 centers in 43 countries entered the run-in period (Fig. 1). Of these, 1771 patients did not fulfill the criteria for randomization, and 48 underwent randomization erroneously or were enrolled at sites that were subsequently closed owing to serious violations of Good Clinical Practice guidelines; these patients were prospectively omitted from all analyses. Accordingly, for the intention-to-treat analysis, 2340 patients were randomly assigned to the combination therapy of enalapril plus aliskiren, 2340 to aliskiren alone, and 2336 to enalapril alone. The percentage of patients in the high-dose stratum for enalapril was 89% in each treatment group. Overall, the treatment groups were balanced with respect to the characteristics at baseline (Table 1). Participants with diabetes at baseline were older and more likely to have ischemic heart disease than were those without diabetes. (For further information, see Tables S2 and S3 in the Supplementary Appendix.)

FOLLOW-UP

Overall, the median follow-up was 36.6 months (interquartile range 22.4 to 52.2), with no significant difference among the three groups. The number of patients who were lost to follow-up for vital status before the completion of the trial (or owing to regulatory censoring with regard to patients with diabetes) was 31 (1.3%) in the combination-therapy group, 19 (0.8%) in the aliskiren group, and 19 (0.8%) in the enalapril group. For patients who did not have data censored for a regulatory reason, follow-up ended on July 31, 2015.

The number of patients who had data censored because of diabetes was 665 (28.4%) in the combination-therapy group, 627 (26.8%) in the aliskiren group, and 652 (27.9%) in the enalapril group. An additional 20, 25, and 18 patients in each group, respectively, had data censored because of other country-specific requests (Fig. 1). In persons without diabetes, the median follow-up was 46.0 months (interquartile range, 28.0 to 56.1); the median follow-up in patients with diabetes was 24.1 months (interquartile range, 15.1 to 33.2).
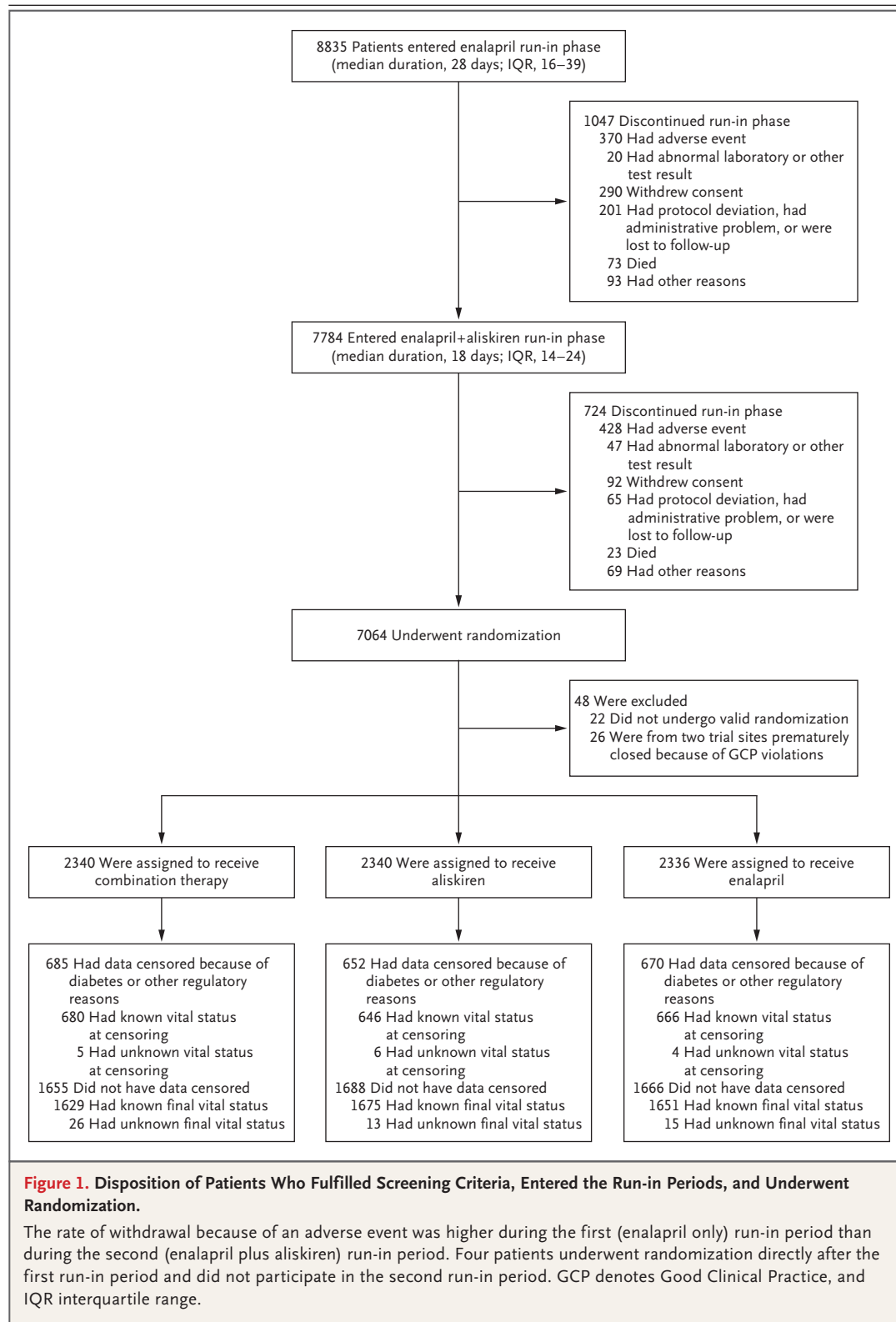
TREATMENT ADMINISTRATION

In persons without diabetes, the trial treatment was discontinued in 741 of 1675 patients (44.2%) in the combination-therapy group, in 693 of 1713 (40.5%) in the aliskiren group, and in 706 of 1684 (41.9%) in the enalapril group for reasons other than death or an administrative reason. The mean percentage of possible treatment time that patients took the trial medication was 77% in the combination-therapy group, 81% in the aliskiren group, and 80% in the enalapril group.

Among patients with diabetes, 211 of 665 patients (31.7%) in the combination-therapy group, 175 of 627 (27.9%) in the aliskiren group, and 209 of 652 (32.1%) in the enalapril group discontinued treatment for reasons other than death or an administrative reason. The mean percentage of possible treatment time that patients took the trial medication was 80%, 84%, and 82%, respectively. (The mean doses of the drugs, according to status with respect to diabetes, are presented in Table S4 in the Supplementary Appendix.)

OUTCOMES

Overall, death from cardiovascular causes or hospitalization for heart failure (the primary outcome) occurred in 770 patients (32.9%) in the combination-therapy group (11.7 events per 100 person-years), in 791 patients (33.8%) in the aliskiren group (12.1 events per 100 person-years), and in 808 patients (34.6%) in the enalapril

Figure 1. Disposition of Patients Who Fulfilled Screening Criteria, Entered the Run-in Periods, and Underwent Randomization.

The rate of withdrawal because of an adverse event was higher during the first (enalapril only) run-in period than during the second (enalapril plus aliskiren) run-in period. Four patients underwent randomization directly after the first run-in period and did not participate in the second run-in period. GCP denotes Good Clinical Practice, and IQR interquartile range.

Table 1. Characteristics of the Patients at Baseline, According to Treatment Group.*

Characteristic	Combination Therapy (N = 2340)	Aliskiren (N = 2340)	Enalapril (N = 2336)
Age — yr	63.2±11.65	63.3±12.06	63.3±11.71
Female sex — no. (%)	494 (21.1)	532 (22.7)	499 (21.4)
Race — no. (%)†			
White	1547 (66.1)	1519 (64.9)	1526 (65.3)
Black	32 (1.4)	37 (1.6)	40 (1.7)
Asian	587 (25.1)	591 (25.3)	586 (25.1)
Other race or missing data	174 (7.4)	193 (8.2)	184 (7.9)
Geographic region — no. (%)			
North America	60 (2.6)	58 (2.5)	59 (2.5)
Latin America	371 (15.9)	377 (16.1)	371 (15.9)
Western Europe	616 (26.3)	620 (26.5)	615 (26.3)
Central Europe	649 (27.7)	646 (27.6)	649 (27.8)
Asia or Pacific region	644 (27.5)	639 (27.3)	642 (27.5)
Cause of heart failure — no. (%)			
Ischemic cardiomyopathy	1335 (57.1)	1295 (55.3)	1300 (55.7)
Nonischemic cardiomyopathy	1005 (42.9)	1045 (44.7)	1036 (44.3)
Left ventricular ejection fraction — %	28.5±5.7	28.4±5.7	28.3±5.7
NYHA functional class — no. (%)‡			
II	1498 (64.0)	1497 (64.0)	1441 (61.7)
III	789 (33.7)	803 (34.3)	849 (36.3)
IV	53 (2.3)	38 (1.6)	46 (2.0)
Physiological measure			
Systolic blood pressure — mm Hg	124±19	124±18	123±18
Heart rate — beats/min	72±13	72±12	72±13
Body-mass index	27.3±5.3	27.4±5.4	27.3±5.3
Laboratory measure			
NT-proBNP — pg/ml§	1193 (640–2351)	1167 (627–2173)	1223 (634–2194)
Estimated GFR — ml/min/1.73 m^2	74±27	74±23	74±22
Medical history — no. (%)			
Hypertension	1447 (61.8)	1460 (62.4)	1425 (61.0)
Diabetes	665 (28.4)	627 (26.8)	652 (27.9)
Atrial fibrillation	801 (34.2)	788 (33.7)	801 (34.3)
Hospitalization for heart failure	1408 (60.2)	1382 (59.1)	1398 (59.8)
Myocardial infarction	975 (41.7)	929 (39.7)	943 (40.4)
Stroke	169 (7.2)	165 (7.1)	158 (6.8)
Medication at randomization — no. (%)			
Digitalis	765 (32.7)	748 (32.0)	729 (31.2)
Diuretic	1869 (79.9)	1852 (79.1)	1877 (80.4)
Beta-adrenergic blocker	2152 (92.0)	2133 (91.2)	2147 (91.9)
Mineralocorticoid antagonist	856 (36.6)	864 (36.9)	882 (37.8)

Table 1. (Continued.)

Characteristic	Combination Therapy (N = 2340)	Aliskiren (N = 2340)	Enalapril (N = 2336)
Device for treating heart failure at screening visit — no. (%)			
Defibrillating device¶	350 (15.0)	362 (15.5)	336 (14.4)
Cardiac-resynchronization therapy	142 (6.1)	120 (5.1)	131 (5.6)

* Plus–minus values are means ±SD. Combination therapy included both aliskiren and enalapril. There were no significant differences among the three groups with respect to any of the characteristics listed. Percentages may not total 100 because of rounding. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate.
† Race was determined by the investigators.
‡ Data for the New York Heart Association (NYHA) class reflect the status of patients at screening; although all patients were required to have at least class II symptoms at screening, one patient in the aliskiren group was in NYHA class I (protocol deviation) and another patient in this group did not have the NYHA class recorded at baseline.
§ Values for the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration were available for 2120 patients in the combination-therapy group, for 2097 in the aliskiren group, and for 2134 patients in the enalapril group.
¶ Defibrillating devices included an implantable cardioverter–defibrillator and implantable cardioverter–defibrillator with cardiac resynchronization.

group (12.4 events per 100 person-years) (Fig. 2A and Table 2). The hazard ratio in the combination-therapy group, as compared with the enalapril group, was 0.93 (95% confidence interval [CI], 0.85 to 1.03; P=0.17); the hazard ratio in the aliskiren group, as compared with the enalapril group, was 0.99 (95% CI, 0.90 to 1.10; P=0.91 for superiority). Although the noninferiority margin of 1.104 was met with the use of the 95% confidence interval, the one-sided P value of 0.0184 did not fulfill the prespecified requirement of a P value of 0.0123 or less. A sensitivity analysis that included only patients who received the assigned trial regimen gave consistent results, as did an analysis in which data that were collected after regulatory censoring were included (Tables S5 and S6 in the Supplementary Appendix).
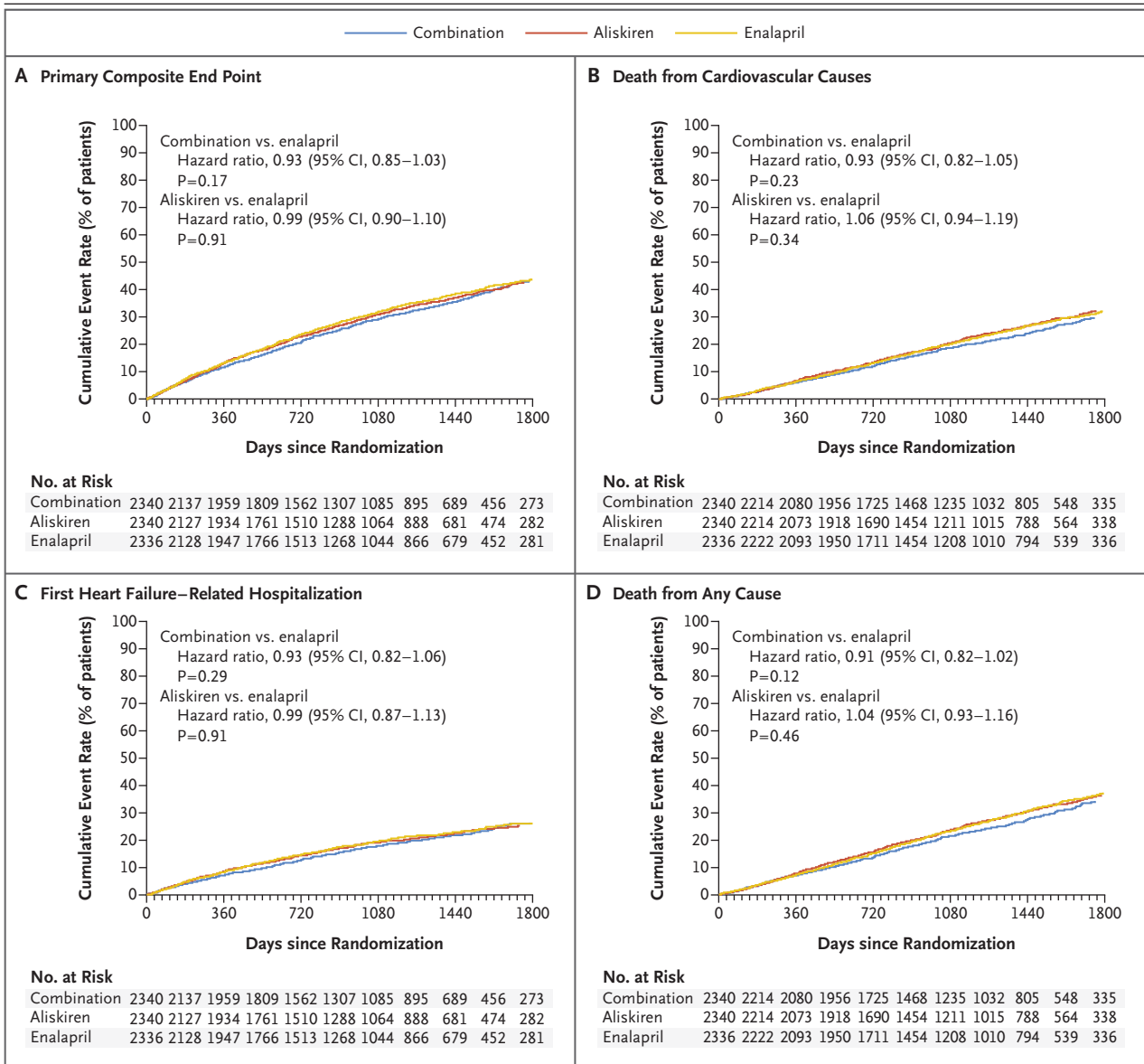
There were no significant between-group differences in the secondary outcome (change in the KCCQ clinical summary score at 12 months) or in selected prespecified exploratory outcomes (Table 2 and Fig. 2). The exploratory composite renal outcome (the composite of death from renal causes, end-stage renal disease, or doubling of the serum creatinine level) occurred significantly more frequently in the combination-therapy group than in the enalapril group (Table 2). At 4 months, 8 months, and 12 months, the decrease from baseline in the NT-proBNP concentration was greater in the combination-therapy group than in the enalapril group. (See also Tables S7 and S8 in the Supplementary Appendix.)

In persons without diabetes, the primary outcome occurred in 574 of 1675 patients (34.3%) in the combination-therapy group (10.6 events per 100 person-years) and in 592 of 1684 patients (35.2%) in the enalapril group (11.1 events per 100 person-years; hazard ratio, 0.96; 95% CI, 0.85 to 1.07; P=0.46). In persons with diabetes, the primary outcome occurred in 196 of 665 patients (29.5%) in the combination-therapy group (16.3 events per 100 person years) and in 216 of 652 patients (33.1%) in the enalapril group (18.8 events per 100 person-years; hazard ratio, 0.86; 95% CI, 0.71 to 1.04; P=0.13; P=0.35 for interaction). The effect of combination therapy as compared with enalapril was consistent for the primary outcome across the prespecified subgroups, as was the effect of aliskiren as compared with enalapril. A similar consistency according to subgroup was seen for the outcome of death from any cause. (See also Figs. S1 and S2 in the Supplementary Appendix.)

SAFETY

Hypotension, renal dysfunction, and hyperkalemia occurred more commonly with combination therapy than with enalapril. The rates of these adverse effects were similar in the aliskiren group and the enalapril group, except for hypotension, which was more common with enalapril

Combination ——— Aliskiren ——— Enalapril

A Primary Composite End Point

Combination vs. enalapril
  Hazard ratio, 0.93 (95% CI, 0.85–1.03)
  P=0.17
Aliskiren vs. enalapril
  Hazard ratio, 0.99 (95% CI, 0.90–1.10)
  P=0.91

No. 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

B Death from Cardiovascular Causes

Combination vs. enalapril
  Hazard ratio, 0.93 (95% CI, 0.82–1.05)
  P=0.23
Aliskiren vs. enalapril
  Hazard ratio, 1.06 (95% CI, 0.94–1.19)
  P=0.34

No. 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

C First Heart Failure–Related Hospitalization

Combination vs. enalapril
  Hazard ratio, 0.93 (95% CI, 0.82–1.06)
  P=0.29
Aliskiren vs. enalapril
  Hazard ratio, 0.99 (95% CI, 0.87–1.13)
  P=0.91

No. 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

D Death from Any Cause

Combination vs. enalapril
  Hazard ratio, 0.91 (95% CI, 0.82–1.02)
  P=0.12
Aliskiren vs. enalapril
  Hazard ratio, 1.04 (95% CI, 0.93–1.16)
  P=0.46

No. 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

Figure 2. Kaplan–Meier Estimates of the Cumulative Rate of the Prespecified Primary Composite Outcome, Its Components, and Death from Any Cause.

Hazard ratios in the time-to-event analyses for the comparison of combination therapy (enalapril plus aliskiren) with enalapril alone and the comparison of aliskiren alone with enalapril alone are shown for the primary composite outcome of death from cardiovascular causes or first hospitalization for heart failure (Panel A), for the primary-outcome components (Panels B and C), and for death from any cause (Panel D). CI denotes confidence interval. The comparison of aliskiren with enalapril for the primary end point was a test for superiority; the test for noninferiority is described in the Results section.

than with aliskiren (Table 3). The increase in the rates of renal dysfunction and hyperkalemia with combination therapy was greater among patients who were being treated with an aldosterone antagonist at baseline than among those who were not (Table S9 in the Supplementary Appendix). The most frequent adverse events and serious adverse events are summarized in Tables S10 and S11 in the Supplementary Appendix.

As compared with the value at randomization, the mean systolic blood pressure at 4 months was significantly lower with combination therapy than with enalapril (difference vs. enalapril, −1.84 mm Hg; 95% CI, −2.70 to −0.98; P<0.001).

Table 2. Protocol-Specified Primary and Secondary Outcomes.*

Outcome	Combination Therapy (N=2340)	Aliskiren (N=2340)	Enalapril (N=2336)	Combination Therapy vs. Enalapril — Hazard Ratio or Difference (95% CI)	P Value	Aliskiren vs. Enalapril — Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome: death from cardiovascular causes or first hospitalization for worsening heart failure — no. (%)	770 (32.9)	791 (33.8)	808 (34.6)	0.93 (0.85 to 1.03)	0.17	0.99 (0.90 to 1.10)	0.91
Death from cardiovascular causes	512 (21.9)	562 (24.0)	547 (23.4)	0.93 (0.82 to 1.05)	0.23	1.06 (0.94 to 1.19)	0.34
First hospitalization for worsening heart failure	430 (18.4)	442 (18.9)	452 (19.3)	0.93 (0.82 to 1.06)	0.29	0.99 (0.87 to 1.13)	0.91
Secondary outcome: change in KCCQ clinical summary score at 12 mo†	−5.04±0.56	−6.03±0.57	−5.01±0.55	−0.03 (−1.56 to 1.50)	0.97	−1.02 (−2.56 to 0.52)	0.20
Other prespecified exploratory outcomes — no. (%)‡							
Death from cardiovascular causes, hospitalization for heart failure, nonfatal myocardial infarction, nonfatal stroke, or resuscitated cardiac arrest	841 (35.9)	874 (37.4)	877 (37.5)	0.94 (0.86 to 1.04)	0.23	1.01 (0.92 to 1.11)	0.80
Fatal or nonfatal myocardial infarction	88 (3.8)	84 (3.6)	100 (4.3)	0.87 (0.66 to 1.16)	0.36	0.85 (0.64 to 1.14)	0.28
Fatal or nonfatal stroke	87 (3.7)	103 (4.4)	93 (4.0)	0.93 (0.70 to 1.25)	0.65	1.12 (0.85 to 1.49)	0.42
First resuscitated cardiac arrest	31 (1.3)	35 (1.5)	32 (1.4)	0.96 (0.58 to 1.57)	0.86	1.10 (0.68 to 1.78)	0.69
Death from any cause	595 (25.4)	654 (27.9)	646 (27.7)	0.91 (0.82 to 1.02)	0.12	1.04 (0.93 to 1.16)	0.46
Composite renal outcome — no. (%)§	39 (1.7)	26 (1.1)	18 (0.8)	2.17 (1.24 to 3.79)	0.007	1.50 (0.82 to 2.74)	0.18

* The comparison of aliskiren with enalapril was a test for superiority. For noninferiority, the one-sided P value was 0.0184, which did not fulfill the prespecified requirement of a P value of 0.0123 or less. For all outcomes other than the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (on a scale from 0 to 100, with higher scores indicating better health-related quality of life), the data are shown as number of patients with an event as a fraction of the number of patients at risk, and the treatment effect is shown as the hazard ratio and the 95% confidence interval (CI), which were calculated with the use of Cox regression models with treatment, dose stratum, and NYHA class (I or II vs. III or IV) as fixed-effect factors and the log-transformed NT-proBNP value at baseline as a covariate. P values are two-sided and were not adjusted for multiple comparisons.
† The KCCQ score was evaluated with the use of a repeated-measures analysis with the baseline value as a covariate and treatment, dose stratum, NYHA class, and a visit-by-treatment interaction; a score of 0 was used in patients who died. The results are shown as the least-square mean change from baseline ±SE, and the treatment effect is shown as the least-square mean of the difference with the 95% confidence interval. Scores were available at 12 months for 1796 patients in the combination-therapy group, for 1811 patients in the aliskiren group, and for 1804 in the enalapril group.
‡ The full list of prespecified exploratory outcomes is provided in Table S1 in the Supplementary Appendix.
§ The composite renal outcome consisted of death from renal causes, end-stage renal disease (initiation of dialysis, renal transplantation, or a serum creatinine concentration of >6.0 mg per deciliter [530 μmol per liter]), or a doubling of serum creatinine from baseline (to more than the upper limit of the normal range) that was sustained for at least 1 month.

Table 3. Prospectively Collected Safety Outcomes during Double-Blind Treatment.*

Variable	Combination Therapy (N = 2340)	Aliskiren (N = 2340)	Enalapril (N = 2336)	P Value	
				Combination Therapy vs. Enalapril	Aliskiren vs. Enalapril
	no. of patients (%)				
Hypotension					
Symptomatic hypotension	322 (13.8)	249 (10.6)	258 (11.0)	0.005	0.67
Symptomatic hypotension with systolic blood pressure <90 mm Hg	87 (3.7)	31 (1.3)	55 (2.4)	0.008	0.009
Renal impairment					
Investigator-reported renal impairment	389 (16.6)	279 (11.9)	306 (13.1)	<0.001	0.23
Serum creatinine†					
≥2.5 mg/dl	95 (4.1)	63 (2.7)	62 (2.7)	0.009	1.00
≥3.0 mg/dl	46 (2.0)	35 (1.5)	29 (1.2)	0.06	0.53
Hyperkalemia					
Investigator-reported hyperkalemia	351 (15.0)	192 (8.2)	243 (10.4)	<0.001	0.01
Serum potassium					
>5.5 mmol/liter	401 (17.1)	255 (10.9)	291 (12.5)	<0.001	0.10
>6.0 mmol/liter	116 (5.0)	70 (3.0)	83 (3.6)	0.02	0.29
Cough	290 (12.4)	241 (10.3)	284 (12.2)	0.83	0.046

* The table shows the numbers and percentages of patients who had the prespecified safety event at any time after randomization until the end of the trial, except for patients with diabetes (and other patients whose treatment was discontinued owing to the protocol amendment or another health-authority request), for whom only data collected up to the censoring date were included. The numbers and percentages of patients who permanently discontinued treatment owing to hypotension-related adverse events were 83 (3.5%) in the combination-therapy group, 37 (1.6%) in the aliskiren group, and 50 (2.1%) in the enalapril group (P=0.005 for the comparison of combination therapy with enalapril; P=0.16 for the comparison of aliskiren with enalapril); for renal impairment–related adverse events, the corresponding values were 143 (6.1%), 97 (4.1%), and 106 (4.5%) (P=0.02 for the comparison of combination therapy with enalapril; P=0.52 for the comparison of aliskiren with enalapril); and for hyperkalemia-related adverse events, the corresponding values were 70 (3.0%), 29 (1.2%), and 31 (1.3%) (P<0.001 for the comparison of combination therapy with enalapril; P=0.80 for the comparison of aliskiren with enalapril).
† To convert values for creatinine to micromoles per liter, multiply by 88.4.

The difference between the mean values in the aliskiren group and the enalapril group was 0.53 mm Hg (95% CI, −0.31 to 1.37; P=0.22).

DISCUSSION

We found that the addition of the renin inhibitor aliskiren to enalapril did not result in a lower risk of death from cardiovascular causes or hospitalization due to heart failure, as compared with enalapril alone, but did cause more hypotension, renal dysfunction, and hyperkalemia, despite the active run-in period that resulted in the exclusion of patients who had these problems on initial exposure to the treatments studied. In our trial, patients with diabetes had the treatment stopped prematurely because of regulatory concern about the safety of aliskiren added to an ACE inhibitor in such persons.[15-19] Because of this, we revised our statistical analysis plan to prespecify examination of the effect of combination therapy, as compared with enalapril alone, in patients without diabetes.[13] This analysis showed the same effect of combination therapy as in the trial overall.

Our findings regarding combination therapy contrast with those of earlier trials involving patients with heart failure in which the addition of an ARB to an ACE inhibitor was of some benefit.[5,6] Although renin inhibition is pharmacologically distinct from angiotensin-receptor blockade, the difference between our trial and the other trials is unlikely to be explained by differences in the treatments used.[9-11] The more

likely explanation is that neither earlier trial required an evidence-based dose of ACE inhibitor, whereas our trial did.

The absence of additional benefit with combination therapy in our study was not due to a lack of incremental inhibition of the renin–angiotensin system, because the addition of aliskiren to enalapril led to more adverse effects that are indicative of greater blockade of this system. A similar excess of adverse effects was noted when only half the full dose of valsartan was added to an evidence-based dose of captopril in patients after myocardial infarction.[7] Collectively, these findings suggest that there is a therapeutic ceiling for blockade of the renin–angiotensin system beyond which there is little or no additional efficacy and only more adverse effects. These findings also argue against the suggestion that the benefit of sacubitril–valsartan over enalapril could be due to more intense blockade of the renin–angiotensin system.[20,21] The lack of benefit of added aliskiren was not due to inadequate statistical power, despite regulatory censoring of data from patients with diabetes (and from some others). Our trial was event-driven, and the required number of patients had a primary outcome. Also, despite the high rate of discontinuation of the randomly assigned therapy by the end of the trial, overall exposure to the treatment was satisfactory.

A notable feature of our trial was the regulatory intervention in which the drug was discontinued in patients with diabetes during the course of the trial.[13] This intervention was based on the findings of possible harm from aliskiren in patients with diabetes in two other trials (ASTRONAUT and ALTITUDE).[15,16,19] Our trial included a large proportion of patients with diabetes, who had exposure to aliskiren for a median of 24 months despite truncated follow-up. We did not identify worse outcomes in the patients with diabetes who were treated with combination therapy than in those who were treated with enalapril alone. Patients with diabetes who were treated with aliskiren monotherapy had outcomes similar to those of patients treated with enalapril. A statement of the data and safety monitoring board of ATMOSPHERE concerning this regulatory intervention has now been published in the *Journal*.[22]

In conclusion, in patients with heart failure and reduced ejection fraction, we found no benefit from the addition of a renin inhibitor to an evidence-based dose of enalapril. Our findings also do not support the use of a renin inhibitor as an alternative to an ACE inhibitor, because the prespecified criterion for noninferiority was not met.

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