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Effect of Aliskiren on Postdischarge Mortality and Heart Failure Readmissions Among Patients Hospitalized for Heart Failure

The ASTRONAUT Randomized Trial

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Importance Hospitalizations for heart failure (HHF) represent a major health burden, with high rates of early postdischarge rehospitalization and mortality.

Objective To investigate whether aliskiren, a direct renin inhibitor, when added to standard therapy, would reduce the rate of cardiovascular (CV) death or HF rehospitalization among HHF patients.

Design, Setting, and Participants International, double-blind, placebo-controlled study that randomized hemodynamically stable HHF patients a median 5 days after admission. Eligible patients were 18 years or older with left ventricular ejection fraction (LVEF) 40% or less, elevated natriuretic peptides (brain natriuretic peptide [BNP] ≥400 pg/mL or *N*-terminal pro-BNP [NT-proBNP] ≥1600 pg/mL), and signs and symptoms of fluid overload. Patients were recruited from 316 sites across North and South America, Europe, and Asia between May 2009 and December 2011. The follow-up period ended in July 2012.

Intervention All patients received 150 mg (increased to 300 mg as tolerated) of aliskiren or placebo daily, in addition to standard therapy. The study drug was continued after discharge for a median 11.3 months.

Main Outcome Measures Cardiovascular death or HF rehospitalization at 6 months and 12 months.

Results In total, 1639 patients were randomized, with 1615 patients included in the final efficacy analysis cohort (808 aliskiren, 807 placebo). Mean age was 65 years; mean LVEF, 28%; 41% of patients had diabetes mellitus, mean estimated glomerular filtration rate, 67 mL/min/1.73 m^2. At admission and randomization, median NT-proBNP levels were 4239 pg/mL and 2718 pg/mL, respectively. At randomization, patients were receiving diuretics (95.9%), β-blockers (82.5%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (84.2%), and mineralocorticoid receptor antagonists (57.0%). In total, 24.9% of patients receiving aliskiren (77 CV deaths, 153 HF rehospitalizations) and 26.5% of patients receiving placebo (85 CV deaths, 166 HF rehospitalizations) experienced the primary end point at 6 months (hazard ratio [HR], 0.92; 95% CI, 0.76-1.12; *P*=.41). At 12 months, the event rates were 35.0% for the aliskiren group (126 CV deaths, 212 HF rehospitalizations) and 37.3% for the placebo group (137 CV deaths, 224 HF rehospitalizations; HR, 0.93; 95% CI, 0.79-1.09; *P*=.36). The rates of hyperkalemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with placebo.

Conclusion and Relevance Among patients hospitalized for HF with reduced LVEF, initiation of aliskiren in addition to standard therapy did not reduce CV death or HF rehospitalization at 6 months or 12 months after discharge.

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INHIBITION OF THE RENIN-ANGIOTENsin-aldosterone system (RAAS) has long been recognized as a life-prolonging therapy for patients with chronic heart failure (HF) with reduced left ventricular ejection fraction (LVEF),[1] and angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) are recommended by all major national guidelines.[2,3] However, although the benefits of these treatments are undisputed, these agents induce a compensatory increase in renin and downstream RAAS intermediaries that may partially offset RAAS blocking effects. Based on this pathophysiological concept of "RAAS escape," multiple trials have demon-

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strated clinical benefits with the simultaneous use of multiple RAAS inhibitors.[4-7]

The direct renin inhibitors (DRIs) represent another pharmacologically distinct method for RAAS blockade with the theoretical benefit of upstream RAAS inhibition at the point of pathway activation. Aliskiren, a first-in-class orally active DRI approved for the treatment of hypertension, has demonstrated a favorable hemodynamic and neurohormonal profile in patients with HF with potential to decrease blood pressure, increase renal blood flow, and reduce natriuretic peptides.[8-10] In the Aliskiren Observation of Heart Failure Treatment (ALOFT) study for patients with chronic HF (New York Heart Association [NYHA] class II-IV), aliskiren administered in addition to standard therapy significantly reduced brain natriuretic peptide (BNP) level and plasma renin activity compared with placebo.[10] Furthermore, aliskiren was associated with a significant reduction in urinary aldosterone excretion, supporting the hypothesis that a DRI strategy may reduce aldosterone escape.

Despite current evidence-based therapies, patients with hospitalization for HF (HHF) face postdischarge mortality and rehospitalization rates as high as 15% and 30%, respectively, within 60 to 90 days.[11-13] Incomplete suppression of the RAAS may contribute to the exceptionally high postdischarge event rate.[14] Therefore, we hypothesized that the addition of a DRI may improve long-term outcomes. The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study was designed to evaluate the effect of in-hospital initiation of aliskiren, in addition to standard therapy, on postdischarge mortality and HF rehospitalization within 6 months in HHF patients with reduced LVEF.

METHODS

The design of the study has been described previously.[15] ASTRONAUT was a prospective, multicenter, randomized, double-blind, placebo-controlled trial that assessed HHF patients after hemodynamic stabilization. Patients were considered eligible if they had a history of chronic HF defined as requiring standard therapy for 30 days or longer prior to the index hospitalization, were 18 years of age or older, had LVEF 40% or less, had elevated levels of natriuretic peptides (BNP ≥400 pg/mL or *N*-terminal pro-BNP [NT-proBNP] ≥1600 pg/mL) at admission, and had signs and symptoms of fluid overload that required hospitalization. Before randomization, patients were required to be hemodynamically stable, defined as systolic blood pressure 110 mm Hg or greater for at least 6 hours and no use of intravenous vasodilators (except nitrates) or intravenous inotropes from the time of hospital presentation to randomization.

Criteria for exclusion included myocardial infarction, cardiac surgery, or stroke within 3 months prior to enrollment; presence of ventricular assist devices or any type of mechanical support; history of a cardiac transplant or listed for transplant at time of enrollment; hemodynamically significant uncorrected primary cardiac valvular disease; right HF due to pulmonary disease; estimated glomerular filtration rate (eGFR) less than 40 mL/min/1.73 m^2; serum sodium level less than 130 mEq/L; serum potassium level greater than 5.0 mEq/L; and comorbid conditions with an expected survival of less than 3 years.

Institutional review board or ethics committee approval was obtained at each site. Potential participants were initially treated with standard therapy, at which time the diagnosis of worsening chronic HF and study eligibility were confirmed (visit 1). After providing written informed consent, hemodynamically stable patients were randomized in a 1:1 ratio to receive 150 mg of aliskiren or placebo daily, in addition to standard therapy, prior to the hospital discharge (visit 2). Standard HF therapy included but was not limited to diuretics, digoxin, ACE inhibitors, ARBs, β-blockers, and MRAs at the discretion of the treating physician. Patient data regarding baseline demographic characteristics, vital signs, other laboratory and diagnostic testing, and enrollment medications were recorded. Self-identified race (ie, white, black, Asian, Native American, Pacific Islander, other) and ethnicity (ie, Hispanic/Latino, Chinese, Indian, Japanese, mixed, other) data were also collected. Data regarding history of comorbid medical conditions were determined and reported by the study investigators.

One week after randomization (visit 3, week 1), patients were assessed for drug safety and tolerability compared with background standard therapy and continued to receive either aliskiren, 150 mg, or placebo. Two weeks after randomization (visit 4, week 2), the study medication was increased to 300 mg of aliskiren or placebo unless the patient could not tolerate the initial medication dose (such as development of low blood pressure, hyperkalemia, or worsening renal function). Patients returned 2 weeks after this dose change (visit 5, week 4) to ensure that the 300-mg dose was well tolerated. Additional study visits were scheduled for months 2, 3, 6, 9, and 12. Electrolyte levels (ie, serum potassium, serum sodium) and renal function (ie, serum creatinine, eGFR) were measured at every visit. Patients not tolerating the 300-mg study medication dose could be down-titrated to the 150-mg dose at the investigators' discretion at any time during the study.

The original study protocol allowed patients to continue receiving the study drug beyond 12 months, although secondary end points were evaluated at 12 months. However, in accordance with protocol amendment 2 (dated July 5, 2010), maximum follow-up time was subsequently limited to 12 months for all patients. When the planned number of events was projected to be accrued, the study was continued until all patients reached a minimum follow-up time of 6 months (protocol amendment 3 dated November 3, 2011).

Study End Points

The primary end point was the first occurrence of cardiovascular (CV) death

or rehospitalization for HF at 6 months (ie, 190 days) after randomization. The key secondary end point was the first occurrence of CV death or rehospitalization for HF within 12 months of randomization. Other secondary end points included first CV event (defined as CV death, HF hospitalization, nonfatal myocardial infarction, nonfatal stroke, and resuscitated sudden death) within 12 months; all-cause mortality within 6 and 12 months; changes from baseline in NT-proBNP level (at months 1, 6, and 12); and quality of life (activities of daily living, assessed by the Kansas City Cardiomyopathy Questionnaire at months 1, 6, and 12). All potential study end points were adjudicated by a blinded clinical event committee (Brigham and Women's Hospital, Harvard Medical School). An independent data monitoring committee was charged to monitor patient safety every 6 months during the trial.

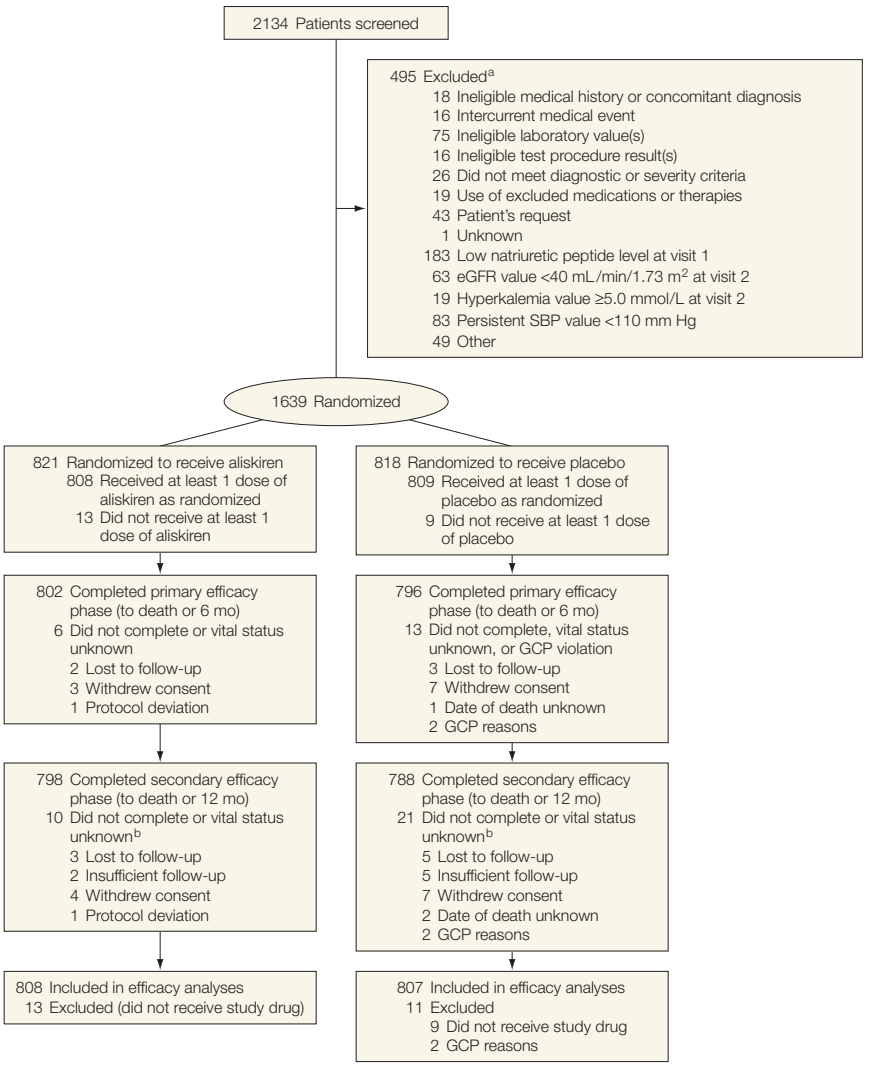
Statistical Analysis

A total of 1782 participants (891 per treatment group) were planned for randomization to reach 381 patients with primary events (ie, CV death or HF rehospitalization within 6 months). This sample size was determined to have 80% power to reject the null hypothesis of equal hazard rates between aliskiren and placebo, assuming exponential survival curves, a 25% event rate in the placebo group at 6 months, a hazard ratio (HR) of 0.75 (25% reduction for superiority of aliskiren vs placebo), a common exponential dropout rate of 10%, and $\alpha = .0495$ (2-sided).[15,16] The calculation of sample size was based on a maximum likelihood comparison of survival curves within 6 months. The 25% event rate was based on the published literature.[17] Given the high event rate in this patient population, the 25% reduction in HR for superiority of aliskiren was deemed to represent a clinically meaningful reduction in events.

A blinded evaluation was planned to assess the observed event rate of the primary end point and to reassess the sample size. All events (ie, number of events and time of event) for the primary end point were included in the interim analysis such that the results were available approximately 1.5 months prior to the completion of the projected recruitment. Because of the unexpected results of the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE)[18] and a subsequent recruitment hold, a blinded sample size review of ASTRONAUT was performed as planned in the protocol and documented in a report from an independent statistician. After this sample size evaluation, it was concluded that the expected number of patients with the primary end point would be achieved with the 1639 patients already randomized. Hence, the study recruitment was stopped early because the required power was projected to have been reached.

The time-to-event data were assumed to follow a proportional hazard model. The null hypothesis was tested at the 2-sided significance level $\alpha = .0495$ using the Cox proportional hazard regression model with treat-

Figure 1. Flow of Patients Through the Trial



eGFR indicates estimated glomerular filtration rate; GCP, Good Clinical Practice; SBP, systolic blood pressure.
[a] Patients could be excluded for multiple reasons.
[b] Numbers are cumulative, in addition to the patients not completing 6 months.

Table 1. Patient Baseline Characteristics[a]

Characteristics	Aliskiren (n = 808)	Placebo (n = 807)	Total (N = 1615)
Age, mean (SD), y	64.7 (12.4)	64.5 (11.9)	64.6 (12.2)
Male sex, No. (%)	637 (78.8)	610 (75.6)	1247 (77.2)
Weight, mean (SD), kg	77.7 (20.4)	78.1 (21.4)	77.9 (20.9)
BMI, mean (SD)[b]	27.1 (6.0)	27.3 (6.3)	27.2 (6.2)
Race, No. (%)			
White	574 (71.0)	566 (70.1)	1140 (70.6)
Black	36 (4.5)	42 (5.2)	78 (4.8)
Asian	167 (20.7)	169 (20.9)	336 (20.8)
Other[c]	31 (3.8)	30 (3.7)	61 (3.8)
Region, No. (%)			
North America	63 (7.7)	61 (7.5)	124 (7.6)
Latin America	83 (10.1)	82 (10.0)	165 (10.1)
Western Europe	203 (24.7)	204 (24.9)	407 (24.8)
Eastern Europe	250 (30.5)	248 (30.3)	498 (30.4)
Asia Pacific and other	222 (27.0)	223 (27.3)	445 (27.2)
Ischemic HF etiology, No. (%)	520 (64.4)	507 (62.8)	1027 (63.6)
NYHA class at admission, No. (%)			
III	498 (61.6)	485 (60.1)	983 (60.9)
IV	310 (38.4)	322 (39.9)	632 (39.1)
NYHA class at randomization, No. (%)			
I/II	284 (35.1)	263 (32.6)	547 (33.9)
III/IV	509 (63.0)	533 (66.0)	1042 (64.5)
Missing NYHA class	15 (1.9)	11 (1.4)	26 (1.6)
Previous HF hospitalization, No. (%)	539 (66.7)	545 (67.5)	1084 (67.1)
LVEF, mean (SD), %	27.9 (7.3)	27.8 (7.2)	27.9 (7.3)
SBP, mean (SD), mm Hg	123.4 (13.4)	123.1 (12.9)	123.3 (13.1)
Heart rate, mean (SD), /min	77.9 (16.0)	77.9 (16.0)	77.9 (16.0)
Atrial fibrillation on ECG, No. (%)	242 (30.0)	244 (30.2)	486 (30.1)
QRS duration, mean (SD), ms	118.6 (39.2)	117.7 (40.7)	118.2 (40.0)
NT-proBNP at admission, pg/mL[d]	4278 (2755-7755)	4183 (2706-7921)	4239 (2710-7886)
NT-proBNP at randomization, pg/mL[d]	2838 (1516-5235)	2674 (1552-5234)	2718 (1531-5235)
BNP at admission, pg/mL[e]	917 (567-1590)	859 (545-1590)	894 (557-1590)
BNP at randomization, pg/mL[e]	474 (239-902)	416 (216-856)	447 (226-879)
Troponin I, median (IQR), ng/mL	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.0 (0.0-0.1)
PRA, median (IQR), μIU/mL	2.85 (0.5-16.6)	3.0 (0.7-16.1)	3.0 (0.6-16.3)
Sodium, mean (SD), mmol/L	138.8 (3.5)	138.8 (3.8)	138.8 (3.7)
Creatinine, mean (SD), mmol/L	99.8 (25.7)	101.0 (28.2)	100.4 (27.0)
BUN, mean (SD), mmol/L	9.1 (3.8)	9.2 (3.8)	9.1 (3.8)
eGFR, mean (SD), mL/min/1.73 m^2	67.3 (20.0)	66.1 (19.9)	66.7 (19.9)
Medical history, No. (%)			
Hypertension	612 (75.7)	613 (76.0)	1225 (75.9)
Coronary artery disease	443 (54.8)	438 (54.3)	881 (54.6)
Atrial fibrillation	337 (41.7)	339 (42.0)	676 (41.9)
Diabetes mellitus	319 (39.5)	343 (42.5)	662 (41.0)
Renal insufficiency	160 (19.8)	172 (21.3)	332 (20.6)
COPD	168 (20.8)	154 (19.1)	322 (19.9)

(continued)

ment and 7 prespecified covariates: log (base2) NT-proBNP (central laboratory measured at baseline), region, age, baseline systolic blood pressure, baseline LVEF, baseline serum creatinine level, and baseline serum sodium level (baseline refers to visit 2). A multiple imputation model was used to impute missing baseline covariates. An estimate of the HR and its associated 2-sided 95% confidence interval were provided by handling of ties with "exact" method from the inference of treatment effect. Kaplan-Meier tabulation was provided for each treatment group. Time-to-event data for secondary end points were analyzed using the same model described for the primary variable. Continuous variables are presented as means with standard deviations, whereas categorical variables are presented as counts and percentages of participants with available data.

All analyses were conducted according to a modified intent-to-treat principle where misrandomized patients were excluded from all efficacy analyses. All patients who received at least 1 dose of the study medication and who were not associated with site-specific Good Clinical Practice (GCP) violations were included in final analyses.

Exploratory analyses were performed for the primary end point and the selected secondary end points (CV death or HF rehospitalization at 12 months, all-cause mortality at 12 months) to assess the consistency of treatment effects across the following subgroups of interest: age with cutoff of 65 and 75 years, sex, race, region, baseline eGFR with 60 mL/min/1.73 m^2 cutoff, NYHA class I/II and III/IV, history of diabetes mellitus (DM), digoxin use, β-blocker use, MRA use, ACE inhibitor or ARB use, use of ACE inhibitor or ARB plus MRA, LVEF, presence of atrial fibrillation, systolic blood pressure, HF etiology, presence of an implantable cardioverter-defibrillator, baseline QRS, baseline NT-proBNP level, baseline plasma renin activity, and baseline troponin I level.

Database management was performed by the sponsor according to a

prespecified analytical plan designed in collaboration with the executive steering committee. All final analyses were conducted by a contract research organization (Pharmaceutical Product Development) using SAS version 9.2 (SAS Institute) and independently by Timothy Collier, BSc, MSc, London School of Hygiene and Tropical Medicine.

RESULTS

Of the 2134 patients screened, 1639 patients were randomized (median time from admission to randomization, 5 days [interquartile range, 3-8 days]; median in aliskiren and placebo groups was 6 and 5 days, respectively) at 316 sites across North America, South America, Europe, and Asia between May 2009 and December 2011. The follow-up period ended in July 2012. A total of 24 patients were excluded from the full analysis set due to either failure to ever receive study treatment or GCP violations at the study site. Therefore, the final cohort for efficacy analyses included 1615 patients (808 assigned to aliskiren, 807 assigned to placebo).

Overall, 98.9% of patients completed the primary efficacy phase (day 190 or death). There were a total of 17 patients (1.1%) with unknown vital status at 6 months and 29 (1.8%) at 12 months or end of the study (FIGURE 1). Median follow-up was 11.3 months (interquartile range, 9.1-12.4 months). The mean age of the study cohort was 64.6 years; mean LVEF, 28%; and mean eGFR, 66.7 mL/min/1.73 m^2. At admission and randomization, median NT-proBNP levels were 4239 pg/mL and 2718 pg/mL, respectively. At randomization, patients were receiving diuretics (95.9%), β-blockers (82.5%), ACE inhibitors or ARBs (84.2%), and MRAs (57.0%).There were no major differences between the 2 treatment groups at the time of randomization (TABLE 1).

Table 1. Patient Baseline Characteristics[a] (continued)

Characteristics	Aliskiren (n = 808)	Placebo (n = 807)	Total (N = 1615)
Background therapies, No. (%)			
Diuretic	775 (95.9)	773 (95.8)	1548 (95.9)
ACE inhibitor/ARB	686 (84.9)	674 (83.6)	1360 (84.2)
β-Blocker	660 (81.7)	673 (83.4)	1333 (82.5)
MRA	448 (55.4)	473 (58.6)	921 (57.0)
Digoxin	319 (39.5)	309 (38.3)	628 (38.9)
ICD	126 (15.6)	127 (15.7)	253 (15.7)
Cardiac resynchronization therapy	55 (6.8)	54 (6.7)	109 (6.7)
Permanent pacemaker	95 (11.8)	86 (10.7)	181 (11.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PRA, plasma renin activity; SBP, systolic blood pressure.

[a] Data collected at the time of patient randomization, unless otherwise specified. No statistically significant difference was seen in any baseline characteristics between aliskiren and placebo groups.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Other category was used when the patient did not meet any of the specified categories.

[d] Median (IQR). Data available for 366 aliskiren and 392 placebo patients at admission and for 778 aliskiren and 776 placebo patients at randomization.

[e] Median (IQR). Data available for 449 aliskiren and 431 placebo patients at admission and for 608 aliskiren and 601 placebo patients at randomization.

Primary End Point

The primary and selected secondary outcomes are summarized in TABLE 2. A total of 201 patients in the aliskiren group (24.9%) and 214 patients in the placebo group (26.5%) experienced the primary end point (HR, 0.92; 95% CI, 0.76-1.12; $P = .41$). The individual components of the primary end point contributed equally to the observed HR for the composite end point (HR, 0.92 and 0.90 for CV death and HF rehospitalization, respectively).

The placebo event rate assumed for the calculation of the original sample size (25% at 6 months) was consistent with the observed value in the placebo group (26.5%). Kaplan-Meier estimates for time to the primary composite end point are depicted in FIGURE 2.

Secondary End Points Within 6 and 12 Months

The key secondary end point of the composite of CV death or HF rehospitalization within 12 months did not differ between the treatment groups. Similarly, there was no statistically significant difference in first CV event (defined as CV death, HF hospitalization, nonfatal myocardial infarction, nonfatal stroke, and sudden death with resuscitation) within 12 months and all-cause death within 6 and 12 months. Although the time to first CV event did not reach statistical significance, events were numerically less frequent in the aliskiren group for the composite and the individual components. In this regard, the myocardial infarction component showed a statistically significant difference in favor of aliskiren ($P = .009$).

During the overall follow-up period (ranging from 0.1 to 31.2 months), the total hospitalization rates (ie, percentage of patients hospitalized for any reason) in the aliskiren and placebo groups were 48.1% and 49.1%, respectively. The HF hospitalization rates within 12 months were 26.2% in the aliskiren group and 27.8% in the placebo group. Slightly higher HF hospitalization rates occurred when examining the entire follow-up period (26.6% and 28.6% in the aliskiren and placebo treatment groups, respectively).

Aliskiren was associated with a statistically significant decrease in NT-proBNP level compared with placebo at each time point tested (months 1, 6, and 12) (eTable 1, available at http://www.jama.com). Mean (SD) changes in systolic blood pressure at 6 and 12 months were −1.46 (18.12) mm Hg and 0.28 (18.06) mm Hg in the aliskiren group and 0.47 (18.38) mm Hg and 1.46 (17.84) mm Hg in the placebo group, respectively. Aliskiren had no significant influence on quality of life ($P > .13$ at each time point tested).

Subgroup Analysis

As shown in FIGURE 3 and the eFigure, for both the primary end point and CV death at 6 months there was no evidence for heterogeneity of treatment effects for any of the subgroups (all treatment × subgroup interactions showed a $P > .05$).

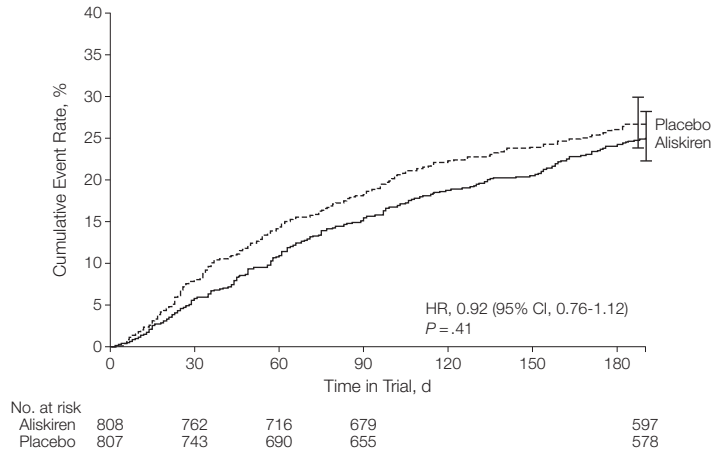
For the secondary 12-month composite end point of CV death and HF rehospitalization, there was a statistically significant interaction with treatment × DM status at baseline (DM group: HR, 1.16; 95% CI, 0.91-1.47; non-DM group: HR, 0.80; 95% CI, 0.64-0.99; $P = .03$ for interaction). For all-cause death by 12 months, there was a statistically significant interaction between treatment and DM status at baseline (DM group: HR, 1.64; 95% CI, 1.15-2.33; non-DM group: HR, 0.69; 95% CI, 0.50-0.94; $P < .001$ for interaction). Among patients with a history of DM, 24.1% of patients died during the double-blind treatment period in the aliskiren group compared with 17.4% patients in the placebo group. In contrast, the rates of death among patients without a history of DM were 15.3% and 20.0% in the aliskiren and placebo groups, respectively. In ASTRONAUT, 41.8% of patients with DM were receiving insulin therapy and 53.2% were receiving oral antihyperglycemic agents. No other significant interactions by treatment groups were seen with other subgroups for the 12-month end points.

Table 2. Summary of Primary and Secondary End Point Results

	No. (%)			
	Aliskiren (n = 808)	Placebo (n = 807)	Hazard Ratio (95% CI)	*P* Value (2-Sided)
Primary End Point: 6 mo				
CV death or HF rehospitalization	201 (24.9)	214 (26.5)	0.92 (0.76-1.12)	.41
CV death	77 (9.5)	85 (10.5)	0.92 (0.68-1.26)	.60
HF rehospitalization	153 (18.9)	166 (20.6)	0.90 (0.72-1.12)	.35
Secondary End Points: 12 mo				
CV death or HF rehospitalization	283 (35.0)	301 (37.3)	0.93 (0.79-1.09)	.36
First CV event	293 (36.3)	321 (39.8)	0.88 (0.75-1.03)	.12
CV death	126 (15.6)	137 (17.0)	0.94 (0.73-1.19)	.60
HF rehospitalization	212 (26.2)	224 (27.8)	0.93 (0.77-1.12)	.44
Fatal or nonfatal MI	18 (2.2)	38 (4.7)	0.47 (0.27-0.83)	.009
Fatal or nonfatal stroke	18 (2.2)	27 (3.3)	0.63 (0.34-1.14)	.13
Resuscitated sudden death	5 (0.6)	10 (1.2)	0.52 (0.18-1.52)	.23
All-cause death	144 (17.8)	148 (18.3)	0.99 (0.78-1.24)	.92

Abbreviations: CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

Figure 2. Kaplan-Meier Analyses of the Cumulative Event Rate for Cardiovascular Death or Heart Failure Hospitalization at 6 Months



For the analysis of events within 6 months, a Cox-regression model was used. Error bars indicate 95% CIs for the Kaplan-Meier estimate at day 190.

Safety

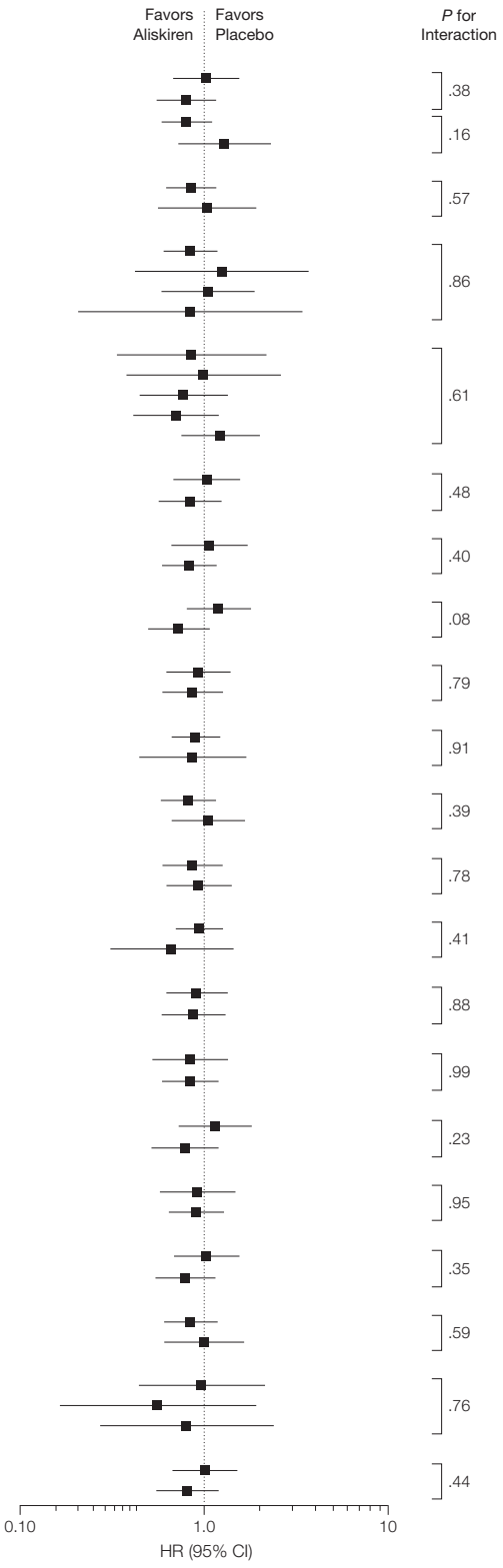
Safety was evaluated in all patients included in the efficacy analysis plus 3 additional placebo patients (1 patient missing informed consent, 2 patients with associated GCP violations, for a total N = 1618). Total numbers of adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, and abnormal laboratory values during the double-blind period are summarized in TABLE 3. There were similar proportions of patients with AEs leading to the discontinuation of the study treatment in both groups and a higher proportion of patients who discontinued the study drug for SAEs in the placebo group (9.8% vs 13.3%, respectively). Discontinuation of the study drug due to nonserious AEs was higher in the aliskiren group (11.8% vs 7.4%). The most frequently reported AEs are summarized in eTable 2.

Patients who received aliskiren were more likely to experience hyperkalemia, hypotension, and renal impairment. Hyperkalemia (>5.5 mmol/L and <6.0 mmol/L) and severe hyperkalemia (≥6.0 mmol/L) were more frequent in the aliskiren group compared with the placebo group (14.3% vs 12.9% and 8.1% vs 5.1%, respectively) (eTable 3). Decrease in the eGFR levels to less than 30 mL/min/1.73 m^2 were also more frequent in the aliskiren group (10.9% vs 9.1%).

The incidences of AEs of interest (hyperkalemia, hypotension, and renal dysfunction) are summarized in Table 3. Hyperkalemia-related AEs were more frequently reported in the aliskiren group compared with the placebo group (20.9% vs 17.5%). The percentage of patients who reported hypotension-related AEs was higher in the aliskiren group than in the placebo group (17.1%

Figure 3. Prespecified Subgroup Analyses Related to the Primary End Point of Cardiovascular Death or Heart Failure Rehospitalization at 6 Mo

Subgroup Variable	No. (%) With End Point		Total No.		HR (95% CI)	*P* for Interaction
	Aliskiren	Placebo	Aliskiren	Placebo		
Age, y						
<65	92 (24.3)	94 (23.8)	378	395	1.01 (0.76-1.35)	.38
≥65	109 (25.3)	120 (29.1)	430	412	0.85 (0.66-1.11)	
<75	149 (23.8)	171 (27.6)	625	619	0.85 (0.69-1.06)	.16
≥75	52 (28.4)	43 (22.9)	183	188	1.19 (0.79-1.78)	
Sex						
Male	162 (25.4)	169 (27.7)	637	610	0.89 (0.72-1.10)	.57
Female	39 (22.8)	45 (22.8)	171	197	1.02 (0.66-1.57)	
Race						
White	132 (23.0)	147 (26.0)	574	566	0.88 (0.70-1.12)	.86
Black	13 (36.1)	14 (33.3)	36	42	1.16 (0.54-2.48)	
Asian	48 (28.7)	45 (26.6)	167	169	1.03 (0.69-1.55)	
Other	8 (25.8)	8 (26.7)	31	30	0.88 (0.33-2.35)	
Region						
North America	17 (27.4)	19 (31.1)	62	61	0.89 (0.46-1.72)	.61
Latin America	17 (21.0)	17 (20.7)	81	82	0.99 (0.50-1.94)	
Western Europe	48 (24.2)	56 (28.4)	198	197	0.83 (0.56-1.22)	
Eastern Europe	50 (20.1)	60 (24.4)	249	246	0.78 (0.53-1.13)	
Asia Pacific	69 (31.7)	62 (28.1)	218	221	1.15 (0.81-1.62)	
Baseline eGFR						
<60 mL/min/1.73 m^2	92 (29.2)	91 (29.0)	315	314	1.02 (0.76-1.36)	.48
≥60 mL/min/1.73 m^2	99 (21.8)	107 (23.8)	454	449	0.88 (0.67-1.16)	
Baseline NYHA						
NYHA I or II	74 (26.1)	65 (24.7)	284	263	1.04 (0.75-1.46)	.40
NYHA III or IV	123 (24.2)	145 (27.2)	509	533	0.87 (0.69-1.11)	
Diabetes mellitus						
Yes	99 (31.0)	100 (29.2)	319	343	1.13 (0.86-1.50)	.08
No	102 (20.9)	114 (24.6)	489	464	0.80 (0.61-1.04)	
Baseline digoxin use						
Yes	98 (27.5)	98 (28.7)	356	342	0.95 (0.71-1.25)	.79
No	103 (22.8)	116 (24.9)	452	465	0.90 (0.69-1.17)	
β-Blockers						
Yes	166 (23.8)	178 (25.8)	698	689	0.93 (0.75-1.15)	.91
No	35 (31.8)	36 (30.5)	110	118	0.90 (0.56-1.44)	
Aldosterone blockers						
Yes	124 (24.5)	141 (27.5)	507	512	0.87 (0.68-1.10)	.39
No	77 (25.6)	73 (24.7)	301	295	1.03 (0.75-1.42)	
Aldosterone blockers + ACEI or ARB						
Yes	108 (23.3)	117 (25.8)	463	454	0.90 (0.69-1.17)	.78
No	93 (27.0)	97 (27.5)	345	353	0.95 (0.72-1.27)	
ACEI or ARB						
Yes	178 (24.3)	182 (25.3)	733	718	0.95 (0.78-1.17)	.41
No	23 (30.7)	32 (36.0)	75	89	0.75 (0.44-1.29)	
Ejection fraction						
≤ Median	103 (26.2)	117 (27.9)	393	419	0.93 (0.72-1.22)	.88
> Median	98 (23.6)	97 (25.1)	415	387	0.91 (0.68-1.20)	
Baseline NT-proBNP						
≤ Median	65 (17.2)	77 (19.3)	379	399	0.88 (0.63-1.22)	.99
> Median	123 (30.8)	131 (34.7)	399	377	0.88 (0.69-1.13)	
Baseline PRA						
≤ Median	80 (24.3)	73 (22.4)	329	326	1.10 (0.80-1.51)	.23
> Median	86 (26.3)	94 (29.0)	327	324	0.84 (0.63-1.13)	
Atrial fibrillation at baseline						
Yes	71 (29.3)	72 (29.6)	242	243	0.94 (0.68-1.31)	.95
No	126 (23.1)	135 (24.7)	546	546	0.93 (0.73-1.18)	
Baseline SBP						
< Median	95 (31.4)	96 (30.9)	303	311	1.02 (0.77-1.35)	.35
≥ Median	106 (21.0)	118 (23.8)	505	495	0.85 (0.65-1.10)	
Heart failure etiology						
Ischemic	140 (26.9)	147 (29.0)	520	507	0.89 (0.70-1.12)	.59
Nonischemic	61 (21.2)	66 (22.1)	288	299	1.00 (0.70-1.41)	
ICD						
ICD	25 (29.8)	27 (28.7)	84	94	0.97 (0.56-1.69)	.76
CRT	9 (17.0)	13 (24.5)	53	53	0.66 (0.28-1.56)	
Both	15 (35.7)	13 (39.4)	42	33	0.85 (0.40-1.83)	
Baseline QRS ≥120 ms						
Yes	98 (27.7)	96 (27.0)	354	355	1.00 (0.76-1.33)	.44
No	97 (22.5)	111 (25.6)	431	433	0.86 (0.65-1.13)	



Median values for variables dichotomized at the median were ejection fraction, 29%; NT-proBNP, 2718 pg/mL; PRA, 3.0 ng/mL/h; SBP, 120 mm Hg.

Table 3. Summary of Adverse Events by Treatment Group (Safety Set)[a]

Patient Characteristic	No. (%) Aliskiren (n = 808)	Placebo (n = 810)	Total (N = 1618)	*P* Value
≥1 AE	670 (82.9)	667 (82.3)	1337 (82.6)	.79
≥1 SAE	421 (52.1)	435 (53.7)	856 (52.9)	.55
Discontinued study drug due to any AEs	171 (21.2)	163 (20.1)	334 (20.6)	.62
Discontinued study drug due to any SAEs	79 (9.8)	108 (13.3)	187 (11.6)	.03
Discontinued study drug due to nonserious AEs	95 (11.8)	60 (7.4)	155 (9.6)	.003
AEs of Special Interest	**No. (%)**		**Aliskiren vs Placebo, RR (95% CI)**	***P* Value**
Incidence rate				
Hyperkalemia[b]	169 (20.9)	142 (17.5)	1.19 (0.98-1.46)	.09
Renal impairment or renal failure[c]	134 (16.6)	98 (12.1)	1.37 (1.08-1.75)	.01
Hypotension[d]	138 (17.1)	102 (12.6)	1.36 (1.07-1.72)	.01
Rate of treatment discontinuation due to AEs				
Hyperkalemia[b]	36 (4.5)	23 (2.8)		.09
Renal impairment or renal failure[c]	32 (4.0)	21 (2.6)		.13
Hypotension[d]	29 (3.6)	19 (2.3)		.15

Abbreviations: AE, adverse event; RR, relative risk; SAE, serious adverse event.
[a] Two aliskiren and 3 placebo deaths were not reported as end points by the investigator due to the early withdrawal of consent.
[b] Includes hyperkalemia and increased blood potassium level.
[c] Includes abnormal results from renal function test, acute renal failure, decreased urine output, increased blood creatinine level, acute prerenal failure, renal impairment, renal failure, decreased glomerular filtration rate, and increased blood urea concentration.
[d] Includes decreased blood pressure, postural dizziness, hypotension, orthostatic hypotension, and procedural hypotension.

vs 12.6%). Adverse events potentially related to renal dysfunction were imbalanced between the aliskiren group and the placebo group (16.6% vs 12.1%).

COMMENT

The ASTRONAUT trial was designed to evaluate the effect of in-hospital initiation of aliskiren after clinical stabilization, in addition to standard therapy, on postdischarge morbidity and mortality in HHF patients with reduced LVEF. Overall, aliskiren therapy had no significant effect on the primary composite end point of CV mortality or rehospitalization for HF at 6 months. Aliskiren treatment also had no effect on 6-month or 12-month clinical end points. However, the addition of aliskiren to standard therapy was associated with significantly larger decreases in NT-proBNP levels during the 12-month follow-up. As expected, AEs of interest (hyperkalemia, hypotension, and renal impairment/renal failure) were more frequent in the aliskiren group compared with the placebo group, in line with the aliskiren mechanism of action.

The RAAS represents a long-established therapeutic target in CV disease, and multiple inhibitors of the pathway have been shown to improve outcomes in chronic HF.[1,4,7,19] However, the inhibition of downstream pathway activity can produce a compensatory rise in plasma renin activity that can competitively overcome RAAS blockade. Aliskiren is a DRI with a favorable neurohormonal and hemodynamic profile that offers the theoretical advantage of RAAS blockade at the most proximal step, thus minimizing the effects of RAAS escape.[8-10]

Given the neurohormonal and hemodynamic perturbations present during and after HF hospitalization,[20,21] it was hypothesized that adding aliskiren to standard therapy would lead to reductions in postdischarge mortality and rehospitalization. The main results of the ASTRONAUT trial do not validate the original hypothesis. The only secondary end point achieved in ASTRONAUT was the change from baseline in NT-proBNP level. Despite a significant and sustained reduction in natriuretic peptide level, a known marker of HF severity, aliskiren did not reduce mortality or rehospitalization rates.[22] It is possible that a beneficial effect on HF progression, as suggested by this long-term improvement in natriuretic peptide level, was offset by potential negative drug-associated effects, perhaps particularly in patients with DM.

The subgroup analysis of the 6-month primary end point did not show heterogeneity for any of the subgroups tested. However, subgroup analyses for 12-month end points of CV death or HF rehospitalization and all-cause death revealed a statistically significant interaction by history of DM. The bidirectional effect of aliskiren on 12-month all-cause death for patients with and without DM is notable given the results of the recent ALTITUDE study in which poor outcomes with aliskiren for patients with DM and concerns regarding renal dysfunction, hyperkalemia, hypotension, and stroke resulted in premature study termination.[18]

While ASTRONAUT did not strictly enroll patients with DM, it failed to reproduce the same pattern of clinical outcomes observed in ALTITUDE, which may suggest the role of chance. The results of ALTITUDE indicated that all components of the primary outcome (including CV death, myocardial infarction, stroke, end-stage renal disease/renal death), with the exception of unplanned hospitalization for HF, were nominally more frequent in the aliskiren group. Moreover, a statistically significant greater number of patients receiving aliskiren experienced

cardiac arrest with resuscitation. In contrast, in ASTRONAUT, nominally fewer aliskiren-treated patients experienced CV death, stroke, myocardial infarction, and resuscitated sudden death compared with placebo-treated patients, with myocardial infarction reaching statistical significance.

The precise reasons underlying the poor outcomes among patients with DM receiving aliskiren are unknown and likely complex but may be related to increased risk of hypotension, hyperkalemia, and worsening renal function with the study drug. The exact mechanisms accounting for adverse outcomes in patients with DM and potentially improved outcomes in patients without DM deserve further analysis. However, irrespective of mechanism, the influence of baseline DM on event rate further highlights the heterogeneity of clinical profiles seen in HHF and suggests a role for further patient stratification in future studies.[23,24] The ongoing long-term Aliskiren Trial of Minimizing Outcomes in Patients with Heart Failure (ATMOSPHERE), which will include data for patients with DM, may provide further insights.[25]

Although the diabetes subgroup findings are intriguing, they must be interpreted with caution because of the well-known statistical limitations (ie, low number of patients by subgroup, multiplicity adjustment).[26] This may be particularly relevant in the specific case of ASTRONAUT, in which the observed findings were not based on the primary end point (where there was no significant subgroup × treatment interaction) but rather on select secondary end points. Hence, the role of chance cannot be excluded.

To our knowledge, ASTRONAUT is the first multicenter, international study that randomized stable, but hospitalized, patients with chronic HF several days after admission (median 5 days). This added time between hospital admission and randomization allowed for clinical and hemodynamic stabilization, as reflected in improvements in NYHA functional class and natriuretic peptide levels. Despite this stabilization and the use of evidence-based therapies, risk of death and rehospitalization remained high.

Prior prospective HF studies have focused primarily on (1) worsening chronic HF requiring hospitalization and short-term acute interventions to treat significant signs, symptoms, and hemodynamic derangements or (2) chronic stable ambulatory patients. ASTRONAUT may serve as the model for future trials in stabilized HHF patients. Given that HF is a chronic condition, a 1- to 2-day in-hospital therapy is unlikely to change the natural history of disease. Rather, a study design similar to ASTRONAUT with in-hospital initiation of therapy for stable patients and subsequent outpatient continuation may offer the best chance of improving outcomes. Moreover, given the persistently high postdischarge event rate confirmed in ASTRONAUT, future HF trials are encouraged to prioritize study of this population over outpatients with chronic HF who have a lower event rate.[27]

CONCLUSIONS

In HHF patients with reduced LVEF, the addition of aliskiren to standard therapy had no significant effect on the primary combined end point of CV mortality or HF rehospitalization at 6 months. The results of the ASTRONAUT study do not support the routine administration of aliskiren, in addition to standard therapy, to patients hospitalized for worsening chronic HF. Subgroup analysis is consistent with previous reports of poor outcomes with the use of aliskiren in patients with DM already taking RAAS inhibitors. Further investigations are needed to evaluate the effects of renin inhibition in a large cohort of HHF patients that excludes patients with DM.

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Role of the Sponsor: Novartis participated in the design, conduct, and management of the study; the collection of the data; and the preparation, review, and approval of the manuscript. Novartis had no role in the analysis and interpretation of the data.

Independent Statistical Analysis: The data were analyzed independently and validated by Timothy Collier, BSc, MSc, who holds an appointment in the Department of Medical Statistics, London School of Hygiene and Tropical Medicine. Mr Collier was given full access to all the raw data, derived data, programs, and output for all the results that would be included in the manuscript. The independent statistical analysis consisted of confirming that the statistical methods used were as prespecified in the protocol and statistical analysis plans; checking the validity of the various analysis patients sets, eg, randomized set, full analysis set, safety set, and derived data; writing and executing programs to carry out the specified statistical analysis; and comparing the results from these analyses with those obtained by Novartis. Mr Collier confirmed that the statistical methods used were as specified in the statistical analysis plan, that the full analysis and safety sets used in the analyses were appropriate, and that the results he obtained were in full agreement with those presented in the manuscript. The independent, validated analysis was fully consistent with that of the sponsor and constitutes the results reported in this article. Mr Collier was remunerated for his work by the sponsor.

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