Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial

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Aims	The objective of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) was to determine whether aliskiren, a direct renin inhibitor, would improve post-discharge outcomes in patients with hospitalization for heart failure (HHF) with reduced ejection fraction. Pre-specified subgroup analyses suggested potential heterogeneity in post-discharge outcomes with aliskiren in patients with and without baseline diabetes mellitus (DM).
Methods and results	ASTRONAUT included 953 patients without DM (aliskiren 489; placebo 464) and 662 patients with DM (aliskiren 319; placebo 343) (as reported by study investigators). Study endpoints included the first occurrence of cardiovascular death or HHF within 6 and 12 months, all-cause death within 6 and 12 months, and change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 1, 6, and 12 months. Data regarding risk of hyperkalaemia, renal impairment, and hypotension, and changes in additional serum biomarkers were collected. The effect of aliskiren on cardiovascular death or HHF within 6 months (primary endpoint) did not significantly differ by baseline DM status ($P = 0.08$ for interaction), but reached statistical significance at 12 months (non-DM: HR: 0.80, 95% CI: 0.64–0.99; DM: HR: 1.16, 95% CI: 0.91–1.47; $P = 0.03$ for interaction). Risk of 12-month all-cause death with aliskiren significantly differed by the presence of baseline DM (non-DM: HR: 0.69, 95% CI: 0.50–0.94; DM: HR: 1.64, 95% CI: 1.15–2.33; $P < 0.01$ for interaction). Among non-diabetics, aliskiren significantly reduced NT-proBNP through 6 months and plasma troponin I and aldosterone through 12 months, as compared to placebo. Among diabetic patients, aliskiren reduced plasma troponin I and aldosterone relative to placebo through 1 month only. There was a trend towards differing risk of post-baseline potassium ≥6 mmol/L with aliskiren by underlying DM status (non-DM: HR: 1.17, 95% CI: 0.71–1.93; DM: HR: 2.39, 95% CI: 1.30–4.42; $P = 0.07$ for interaction).
Conclusion	This pre-specified subgroup analysis from the ASTRONAUT trial generates the hypothesis that the addition of aliskiren to standard HHF therapy in non-diabetic patients is generally well-tolerated and improves post-discharge outcomes and biomarker profiles. In contrast, diabetic patients receiving aliskiren appear to have worse post-discharge outcomes. Future prospective investigations are needed to confirm potential benefits of renin inhibition in a large cohort of HHF patients without DM.
Keywords	Aliskiren • Diabetes • Outcomes • Post-discharge

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Introduction

There are over 1 million primary hospitalizations for heart failure (HHF) annually in the USA alone,[1] and this population continues to experience poor post-discharge outcomes despite available therapies.[2] The heterogeneity of clinical profiles among these patients is well established and the majority have a history of cardiovascular (CV) and non-CV comorbidities.[2,3] Approximately 40% of HHF patients have a history of diabetes mellitus (DM) and observational and clinical trial data have explored the associated prognostic implications.[4,5]

Recently, the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) confirmed the high prevalence of DM among HHF patients with reduced left ventricular ejection fraction (LVEF).[6] In this study, the addition of aliskiren to standard therapy had no significant effect on CV death or heart failure (HF) rehospitalization within 6 or 12 months. Although the overall study results were neutral, pre-specified subgroup analysis found the effect of the study drug on all-cause death within 12 months to differ by the presence of comorbid DM, with aliskiren associated with a higher risk of death in diabetics and lower risk of death in non-diabetics. These data were consistent with previous reports of poor outcomes with aliskiren in diabetics already taking renin−angiotensin−aldosterone system (RAAS) inhibitors.[7] The ASTRONAUT trial affords the opportunity to perform an in-depth characterization of patients with HHF by the presence or absence of DM to better understand this possible bidirectional effect of aliskiren on outcomes. Given the potentially improved survival with aliskiren among nearly 60% of ASTRONAUT patients without diabetes and the current lack of therapies proven to improve outcomes in HHF, these data deserve further analysis.

Methods

Study design

The study design[8] and primary results of the ASTRONAUT trial have been previously described.[6] Briefly, the ASTRONAUT trial was a prospective, multicentre, multinational, randomized, double-blind, placebo-controlled trial investigating the role of oral aliskiren, a direct renin inhibitor, on outcomes among HHF patients. Patients were randomized a median 5 days after hospital admission to 150 mg daily (increased to 300 mg daily as tolerated) of aliskiren or placebo, in addition to standard therapy. All patients were 18 years of age or older with LVEF $\leq$ 40%, elevated natriuretic peptides [B-type natriuretic peptide (BNP) $\geq$ 400 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) $\geq$ 1600 pg/mL], and signs and symptoms of fluid overload that necessitated hospitalization. Before randomization, patients were required to be haemodynamically stable, defined as systolic blood pressure $\geq$ 110 mmHg for at least 6 h and no use of intravenous vasodilators (except nitrates) or intravenous inotropes from time of hospital presentation to randomization. Exclusion criteria included estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2, serum potassium level >5.0 mEq/L, hyponatraemia <130 mEq/L, recent myocardial infarction (MI), cardiac surgery or stroke, and comorbid conditions with expected survival <3 years. Local institutional review boards or ethics committees at each centre approved the study protocol and patients provided written informed consent for participation. Efficacy analysis by patient history of DM (as determined by the investigator) was a protocol pre-specified subgroup analysis prospectively planned prior to database lock and included

all patients from both treatment arms used for efficacy analysis. Safety analysis by baseline DM status was performed *post hoc*.

The primary endpoint in ASTRONAUT was the first occurrence of CV death or HF rehospitalization within 6 months after randomization. Secondary endpoints included CV death or HF rehospitalization within 12 months (key secondary endpoint), first CV event (defined as CV death, HF rehospitalization, non-fatal MI, non-fatal stoke, and resuscitated sudden death) within 12 months, all-cause death within 6 and 12 months, and change from baseline in NT-proBNP level at 1, 6, and 12 months. Additional data regarding biomarker levels (plasma renin activity, plasma troponin I, plasma aldosterone) were also collected and analysed. An independent, clinical events committee adjudicated specific causes of death and hospitalization (Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA).

Statistical analysis

Categorical variables are reported as number (percentage), while continuous variables are expressed as means $\pm$ standard deviation if normally distributed or as median (inter-quartile range) if not normally distributed.

The time-to-event data were assumed to follow a proportional hazard model and hazard ratios (HR) and corresponding 95% confidence intervals (CI) are provided. The assumption of proportional hazards was verified using a Cox proportional hazards regression model which included treatment and a time-dependent explanatory variable created through the interaction between log time and treatment. The estimate of the interaction term was presented in terms of the change in effect from 1 month to the next. In addition, a plot of the log−log survivor function vs. log time for each treatment group was performed. Approximate parallelism between the curves for treatment groups provided supportive evidence of the proportional hazards assumption. Analyses were performed for the primary endpoint and the selected secondary endpoints (CV death or HF rehospitalization within 12 months, all-cause death within 6 and 12 months, first CV event within 12 months). Testing for interaction between all endpoints and baseline DM status was performed. Cumulative event rate estimates (1 − estimated survival function, described in %) vs. time of follow-up (in years) were calculated based on the Kaplan−Meier estimates.

Biomarker data were analysed for diabetic and non-diabetic groups, and changes in NT-proBNP (pg/mL), plasma renin activity (ng/mL/h), plasma troponin I (ng/mL), and plasma aldosterone (pmol/L) were calculated using log-transformation and summarized in a geometric mean with 95% CI on a geometric mean. In addition, a repeated measurement model was performed on change from baseline log-transformed for biomarker variables. All the results were back-transformed to provide the geometric least squares means (presented as a ratio to baseline), the ratio for aliskiren vs. placebo, and the 95% CI around the ratio for each time point (1, 6, and 12 months).

Adverse events of special interest including hyperkalaemia, renal impairment or renal failure, and hypotension and corresponding rates of treatment discontinuation for these events were calculated. Additionally, incidence of post-baseline potassium $\geq$ 6 mmol/L and eGFR <30 mL/min/1.73 m^2 were summarized by treatment group. Relative risk and corresponding 95% CI were used in treatment comparison, and interaction analysis was performed by baseline DM status.

The cohort used for efficacy analysis was from the full-analysis set, defined as all randomized patients who received at least 1 dose of the study drug. Following the intent-to-treat principle, patients were analysed according to the treatment assigned at randomization. Safety was analysed in all patients who received study drug and had at least one post-baseline safety assessment. All statistical analyses were

Table 1 Baseline characteristics of non-diabetic and diabetic patients

Characteristic	Non-diabetics		Diabetics	
	Aliskiren (n = 489)	Placebo (n = 464)	Aliskiren (n = 319)	Placebo (n = 343)
Age (years), mean (SD)	64.1 (13.3)	63.4 (13.0)	65.6 (11.0)	66.0 (10.1)
Male, n (%)	394 (80.6)	345 (74.4)	243 (76.2)	265 (77.3)
Race, n (%)				
Caucasian	342 (69.9)	325 (70.0)	232 (72.7)	241 (70.3)
Black	22 (4.5)	24 (5.2)	14 (4.4)	18 (5.2)
Asian	101 (20.7)	94 (20.3)	66 (20.7)	75 (21.9)
Other	24 (4.9)	21 (4.5)	7 (2.2)	9 (2.6)
NYHA class at Visit 1, n (%)				
III	304 (62.2)	281 (60.6)	194 (60.8)	204 (59.5)
IV	185 (37.8)	183 (39.4)	125 (39.2)	139 (40.5)
NYHA class at Visit 2, n (%)				
I	14 (2.9)	9 (1.9)	3 (0.9)	8 (2.3)
II	166 (33.9)	152 (32.8)	101 (31.7)	94 (27.4)
III	268 (54.8)	258 (55.6)	173 (54.2)	204 (59.5)
IV	35 (7.2)	38 (8.2)	33 (10.3)	33 (9.6)
Ischaemic heart failure aetiology, n (%)	287 (58.7)	248 (53.4)	233 (73.0)	259 (75.5)
Prior heart failure hospitalization, n (%)	309 (63.2)	313 (67.5)	230 (72.1)	232 (67.6)
Ejection fraction (%), mean (SD)	28 (7.3)	27 (7.5)	28 (7.3)	28 (6.9)
Systolic blood pressure (mmHg), mean (SD)	123 (12.8)	123 (12.2)	125 (14.2)	124 (13.8)
Heart rate (b.p.m.), mean (SD)	77 (16.0)	78 (16.5)	79 (16.0)	78 (15.3)
eGFR (mL/min/1.73 m^2), mean (SD), Visit 2	68.5 (20.4)	67.0 (19.9)	65.5 (19.1)	64.9 (20.0)
eGFR (mL/min/1.73 m^2) group, n (%), Visit 2				
<60	181 (37.0)	169 (36.4)	137 (42.9)	146 (42.6)
≥60	291 (59.5)	275 (59.3)	166 (52.0)	183 (53.4)
NT-proBNP (pg/mL), median (IQR), Visit 1	4471 (2840–8540)	4472 (2715–8924)	4015 (2615–6679)	3738 (2682–7461)
NT-proBNP (pg/mL), median (IQR), Visit 2	2851 (1510–5344)	2651 (1555–5257)	2736 (1523–5097)	2699 (1536–5074)
BNP (pg/mL), mean (IQR), Visit 1	936 (592–1650)	842 (533–1570)	908 (541–1567)	866 (558–1655)
BNP (pg/mL), mean (IQR), Visit 2	466 (239–900)	437 (220–910)	480 (238–920)	390 (206–773)
Sodium (mmol/L), mean (SD)	139 (3.7)	139 (3.8)	139 (3.3)	138 (3.8)
Potassium (mmol/L), mean (SD)	4.3 (0.8)	4.3 (0.7)	4.3 (0.5)	4.3 (0.6)
Troponin I (ng/mL), median (IQR)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.1)
Atrial fibrillation on ECG, n (%), Visit 2	154 (31.5)	148 (31.9)	88 (27.6)	96 (28.0)
Medical history, n (%)				
Hypertension	353 (72.2)	330 (71.1)	259 (81.2)	283 (82.5)
Coronary artery disease	240 (49.1)	203 (43.8)	203 (63.6)	235 (68.5)
Renal insufficiency	67 (13.3)	79 (17.0)	93 (29.2)	93 (27.1)
Chronic obstructive pulmonary disease	97 (19.8)	78 (16.8)	71 (22.3)	76 (22.2)
Background therapies, n (%)				
Diuretic (not including mineralocorticoid receptor antagonist)	469 (95.9)	445 (95.9)	306 (95.9)	328 (95.6)
Angiotensin-converting enzyme inhibitors	324 (66.3)	318 (68.5)	203 (63.6)	211 (61.5)
Angiotensin II receptor blockers	87 (17.8)	65 (14.0)	72 (22.6)	80 (23.3)
Beta-blockers	385 (78.7)	391 (84.3)	275 (86.2)	282 (82.2)
Mineralocorticoid receptor antagonist	276 (56.4)	281 (60.6)	172 (53.9)	192 (56.0)

BNP, B-type natriuretic peptide; b.p.m., beat per minute; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.
Data pertain to Visit 2 unless otherwise specified. Visit 1 refers to time point when the diagnosis of worsening chronic heart failure and study eligibility were confirmed. Visit 2 refers to time point when stabilized patients were randomized to aliskiren or placebo, in addition to standard therapy.

Table 2 Study endpoints by baseline diabetes status

Endpoint	Aliskiren, n (%) Non-DM (n = 489) DM (n = 319)	Placebo, n (%) Non-DM (n = 464) DM (n = 343)	Hazard ratio (95% CI)	P for interaction (two-sided)
Primary endpoint (6 months)				
CV death or HF rehospitalization				
Non-DM	102 (20.9)	114 (24.6)	0.80 (0.61–1.04)	
DM	99 (31.0)	100 (29.2)	1.13 (0.86–1.50)	0.08
Secondary endpoints (12 months, unless otherwise specified)				
CV death or HF rehospitalization				
Non-DM	148 (30.3)	165 (35.6)	0.80 (0.64–0.99)	
DM	135 (42.3)	136 (39.7)	1.16 (0.91–1.47)	0.03
First CV event				
Non-DM	154 (31.5)	177 (38.1)	0.75 (0.61–0.94)	
DM	139 (43.6)	144 (42.0)	1.11 (0.88–1.40)	0.02
All-cause death (6 months)				
Non-DM	43 (8.8)	51 (11.0)	0.75 (0.50–1.13)	
DM	42 (13.2)	38 (11.1)	1.38 (0.88–2.15)	0.05
All-cause death				
Non-DM	72 (14.7)	91 (19.6)	0.69 (0.50–0.94)	
DM	72 (22.6)	57 (16.6)	1.64 (1.15–2.33)	<0.01

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure.

performed using SAS version 9.2 (SAS Institute), and two-sided $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

The current study included 1615 patients from the final ASTRO-NAUT efficacy analysis cohort, of which 953 patients were without a documented history of DM (59%). The median follow-up in the overall population was 11.3 months (inter-quartile range 9.1–12.4 months). *Table 1* describes the baseline demographic, clinical, and laboratory profile for all patients in this analysis by underlying DM history and treatment group. Baseline characteristics by treatment arm did not significantly differ by DM status with the following exceptions: age, ischaemic HF aetiology, systolic blood pressure, eGFR, serum sodium, and angiotensin II receptor blocker (ARB) use. Among patients with DM, 42% were receiving insulin therapy and 53% were receiving oral antihyperglycemic agents.

Study endpoints

Outcome analyses for non-diabetic and diabetic patients are displayed in *Table 2*. Overall, the influence of aliskiren on the primary endpoint of CV death or HF rehospitalization within 6 months did not significantly differ by DM status ($P = 0.08$ for interaction). The effect of aliskiren on 12-month CV death or HF rehospitalization ($P = 0.03$ for interaction), first CV event within 12 months ($P = 0.02$ for interaction) and 12-month all-cause death ($P < 0.01$ for interaction) significantly differed according to baseline history

of DM. There was a borderline significant interaction between treatment arm and diabetes status for all-cause death within 6 months ($P = 0.05$ for interaction).

Among non-diabetics, 102 patients in the aliskiren group (20.9%) and 114 patients in the placebo group (24.6%) experienced the primary endpoint (HR: 0.80; 95% CI: 0.61–1.04) (*Figure 1*). In regard to 12-month secondary endpoints, non-diabetics receiving aliskiren were significantly less likely to experience CV death or HF hospitalization (HR: 0.80; 95% CI: 0.64–0.99), first CV event (HR: 0.75; 95% CI: 0.61–0.94) and all-cause death (HR: 0.69; 95% CI: 0.50–0.94) when compared with placebo (*Figure 2*).

Similar to the non-diabetic group, there was no significant difference in the rate of the primary endpoint between treatment groups among patients with DM (HR: 1.13; 95% CI: 0.86–1.50). However, diabetics receiving aliskiren were significantly more likely to die within 12 months (HR: 1.64; 95% CI: 1.15–2.33).

Adjudicated causes of death

Table 3 presents descriptive data on adjudicated causes of death by treatment arm and DM status for all the patients included in efficacy analysis plus three additional placebo patients (one patient missing informed consent, two patients with associated Good Clinical Practice violations). During the double-blind period, the rates of CV death among non-diabetics receiving aliskiren and placebo were 13.7 and 18.9%, respectively. Major contributors to reduced CV death with aliskiren were decreased rates of pump failure (aliskiren 4.7%; placebo 7.1%) and presumed CV death (aliskiren 0.8%; placebo 2.2%). In contrast, among diabetic patients, aliskiren was associated
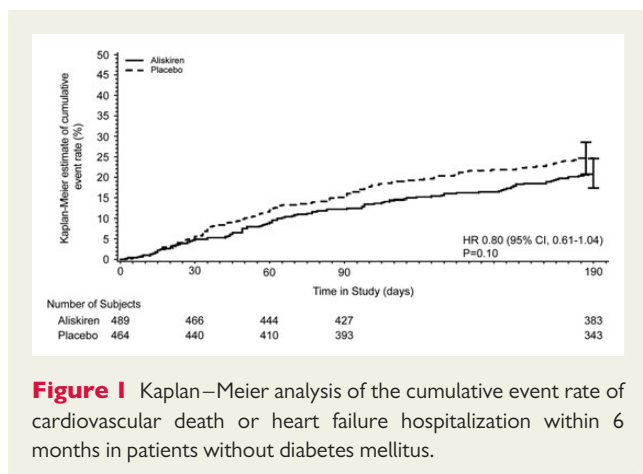
Figure 1 Kaplan–Meier analysis of the cumulative event rate of cardiovascular death or heart failure hospitalization within 6 months in patients without diabetes mellitus.
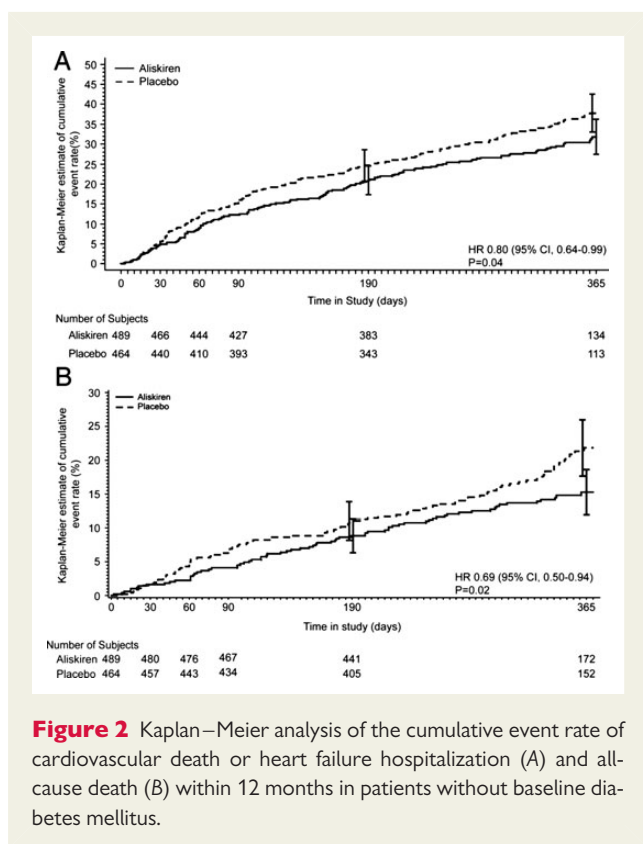

Figure 2 Kaplan–Meier analysis of the cumulative event rate of cardiovascular death or heart failure hospitalization (*A*) and all-cause death (*B*) within 12 months in patients without baseline diabetes mellitus.

with a higher rate of CV death (aliskiren 21.0%; placebo 16.2%), pump failure (aliskiren 9.7%; placebo 6.7%) and sudden death (aliskiren 5.6%; placebo 4.3%). Rates of non-CV death in ASTRONAUT were low in both non-diabetic and diabetic patients.

Effect on biomarkers

The effects of aliskiren on CV biomarkers in patients with and without baseline DM are displayed in *Table 4*. Among non-diabetics, aliskiren was associated with a statistically significant greater decrease in NT-proBNP level compared with placebo at 1 and 6 months post-randomization ($P \leq 0.02$), but not 12 months ($P = 0.08$) (*Figure 3*). Plasma renin activity was significantly reduced with aliskiren at each

time point tested (all $P < 0.01$). Similarly, aliskiren reduced plasma aldosterone and plasma troponin I levels across all time points, relative to placebo (all $P \leq 0.04$).

By comparison, among diabetics, aliskiren was not associated with a decrease in NT-proBNP compared with placebo at any time point tested (all $P \geq 0.10$). Aliskiren significantly reduced plasma aldosterone at 1 month relative to placebo ($P = 0.01$), but not at 6 or 12 months ($P \geq 0.23$). Likewise, diabetics treated with aliskiren had significant decreases in troponin I at 1 month compared to placebo ($P = 0.02$), but not at other time points ($P \geq 0.08$). Similar to patients without DM, diabetics had significant reductions in plasma renin activity at each time point tested relative to placebo (all $P < 0.01$).

Safety

Table 5 displays data for adverse events of special interest among non-diabetic and diabetic patients. There was a trend towards differing risk of post-baseline potassium level ≥ 6 mmol/L with aliskiren by underlying DM status (non-DM: HR: 1.17, 95% CI: 0.71−1.93; DM: HR: 2.39, 95% CI: 1.30−4.42; $P = 0.07$ for interaction). No other notable interactions were seen (all $P \geq 0.32$ for interaction).

Among non-diabetics, aliskiren was associated with significantly higher rates of investigator-reported renal impairment and hypotension, but there was no significant difference in rates of treatment discontinuation due to these adverse effects. When objective cutoffs were used to evaluate post-baseline risk of severe hyperkalaemia (potassium ≥ 6 mmol/L) or severe renal impairment (eGFR < 30 mL/min/1.73 m^2), no significant differences between aliskiren and placebo were seen.

In contrast to non-diabetics, patients with DM who received aliskiren did not demonstrate a higher risk of investigator reported hyperkalaemia, renal impairment, or hypotension, nor did they have an increased risk of study drug discontinuation for these effects. However, using objective measures, diabetic patients were at significantly increased risk of post-baseline severe hyperkalaemia, but not severe renal impairment.

Discussion

In the ASTRONAUT trial, nearly 60% of patients had no history of DM. At baseline, $> 80\%$ of patients were receiving an angiotensin-converting enzyme (ACE) inhibitor/ARB and $> 50\%$ were receiving a mineralocorticoid receptor antagonist (MRA). The effect of aliskiren on the primary endpoint of CV death or HF rehospitalization within 6 months did not significantly differ by baseline DM status. However, analysis of 12-month CV death or HF rehospitalization and all-cause death revealed statistically significant interactions by baseline DM status with non-diabetic patients tending to experience favourable outcomes. Among non-diabetics, aliskiren significantly reduced NT-proBNP through 6 months and plasma renin activity, troponin I and aldosterone through 12 months, as compared to placebo. There was a trend towards interaction favouring less risk of post-baseline potassium ≥ 6 mmol/L with aliskiren in non-diabetics as compared to diabetics.

While the above findings regarding HHF patients without DM may be considered encouraging, they must be viewed in the context of a subgroup analysis and the corresponding statistical limitations,

Table 3 Adjudicated causes of death among non-diabetic and diabetic patients

Adjudicated cause of death, n (%)	Non-diabetics		Diabetics	
	Aliskiren (n = 489)	Placebo (n = 465)	Aliskiren (n = 319)	Placebo (n = 345)
CV death	67 (13.7)	88 (18.9)	67 (21.0)	56 (16.2)
Fatal myocardial infarction	3 (0.6)	6 (1.3)	1 (0.3)	6 (1.7)
Pump failure	23 (4.7)	33 (7.1)	31 (9.7)	23 (6.7)
Sudden death	28 (5.7)	30 (6.5)	18 (5.6)	15 (4.3)
Presumed sudden death	3 (0.6)	1 (0.2)	4 (1.3)	2 (0.6)
Presumed CV death	4 (0.8)	10 (2.2)	7 (2.2)	4 (1.2)
Other CV death	0	0	0	2 (0.6)
Fatal stroke	3 (0.6)	5 (1.1)	3 (0.9)	2 (0.6)
CV procedural	1 (0.2)	0	0	1 (0.3)
Unknown	2 (0.4)	3 (0.7)	3 (0.9)	1 (0.3)
Non-CV death	8 (1.6)	5 (1.1)	10 (3.1)	4 (1.2)
Accidental	1 (0.2)	0	3 (0.9)	0
Pulmonary	0	0	1 (0.3)	0
Infection	3 (0.6)	1 (0.2)	6 (1.9)	2 (0.6)
Malignancy	2 (0.4)	1 (0.2)	0	0
Gastrointestinal	1 (0.2)	3 (0.7)	0	2 (0.6)
Renal	0	0	0	0
Other non-CV death	1 (0.2)	0	0	0

CV, cardiovascular.

including a smaller number of patients per treatment group and issues with multiplicity.[9] However, this efficacy analysis was protocol pre-specified. Furthermore, although the ASTRONAUT protocol planned for the analysis of >26 subgroups of interest, stratifying patients by underlying DM status was the only analysis to demonstrate a statistically significant interaction of $P < 0.05$, albeit for secondary, not primary, endpoints. While the number of pre-specified subgroups tested supports the possibility of one or two groups reaching statistical significance by chance alone, the diabetes findings in ASTRONAUT are consistent with previous prospective data with aliskiren,[7] thus making coincidence less likely.

Our data extend the current body of knowledge in multiple ways and serve to generate hypotheses regarding an underlying mechanism for a potential differential impact of aliskiren on outcomes by DM status. One potential explanation relates to differences in safety profile. Our results suggest that in non-diabetic patients, there was a discrepancy between the subjective and objective risk of the three adverse events of special interest. Although investigators were more likely to report renal impairment and hypotension in patients receiving aliskiren, they were no more likely to discontinue the drug due to these effects, perhaps suggesting they were not severe. Moreover, rates of post-baseline severe hyperkalaemia and renal impairment, as assessed by objective laboratory cutoffs, were no different between treatment arms. These findings contrast with those of the diabetic cohort where incidence of subjective, investigator reported adverse events of special interest and corresponding rates of drug discontinuation did not differ by treatment, yet a greater risk of post-baseline potassium ≥6 mmol/L was seen with

aliskiren with a trend towards interaction by DM status. Existing data in diabetics suggest that hyperkalaemia, hypotension, and worsening eGFR with RAAS blockade predict poor prognosis.[10,11] In ASTRONAUT, it is possible that an increased incidence of hyperkalaemia in diabetics receiving aliskiren, in addition to standard therapy including an ACE inhibitor/ARB, beta-blocker and MRA, contributed to poor outcomes by overshadowing any positive effects of the drug. Likewise, lack of severe hyperkalaemia in non-diabetics may have allowed favourable effects of the drug to predominate.

A second possible mechanism for improved outcomes with aliskiren in non-diabetics is the corresponding biomarker profile. Most notably, among non-diabetics, aliskiren significantly reduced NT-proBNP and plasma aldosterone levels compared with placebo through 6 months. This effect on plasma aldosterone was sustained and significant at 12 months. In diabetic patients, relative to placebo, aldosterone was only significantly reduced at 1 month and NT-proBNP was not significantly reduced at any follow-up time point. Given that NT-proBNP levels were significantly decreased over 12 months in the overall ASTRONAUT cohort without improvements in patient outcomes, it is unlikely that the effect of aliskiren on natriuretic peptides alone is responsible for the potential bidirectional effect of aliskiren by DM status.[6] Rather, it is noteworthy that although absolute levels of plasma aldosterone tended to rise over time in all patients, this rise was blunted in non-diabetic patients receiving aliskiren. This significant sustained ability of aliskiren to attenuate increases in aldosterone, the final downstream neurohormone in the RAAS, may have contributed to the lower event rates in non-diabetics receiving the drug.[12] This hypothesis is consistent

Table 4 Change from baseline in biomarkers among diabetic and non-diabetic patients

Time point	Treatment	Non-diabetic patients			Diabetic patients		
		n	Ratio: endpoint/ baseline; adjusted geometric mean (95% CI)	Ratio: aliskiren/ placebo (95% CI)	n	Ratio: endpoint/baseline; adjusted geometric mean (95% CI)	Ratio: aliskiren/ placebo (95% CI)
NT-proBNP (pg/mL)							
Month 1	Aliskiren	405	0.82 (0.76, 0.89)		264	0.92 (0.85−0.99)	
	Placebo	388	0.93 (0.86, 1.01)	0.88 (0.80, 0.97)	287	0.98 (0.91−1.06)	0.94 (0.85−1.03)
Month 6	Aliskiren	354	0.61 (0.55, 0.68)		215	0.70 (0.62−0.78)	
	Placebo	324	0.74 (0.66, 0.83)	0.83 (0.71, 0.97)	232	0.79 (0.71−0.88)	0.88 (0.76−1.03)
Month 12	Aliskiren	281	0.58 (0.51, 0.66)		166	0.70 (0.60−0.81)	
	Placebo	237	0.68 (0.60, 0.78)	0.85 (0.71, 1.02)	188	0.83 (0.72−0.96)	0.84 (0.68−1.03)
Plasma renin activity (ng/mL/h)							
Month 1	Aliskiren	306	0.15 (0.12−0.18)		216	0.17 (0.13−0.21)	
	Placebo	287	1.54 (1.28−1.85)	0.10 (0.08−0.12)	220	1.20 (0.95−1.50)	0.14 (0.10−0.19)
Month 6	Aliskiren	259	0.16 (0.13−0.20)		168	0.20 (0.15−0.25)	
	Placebo	246	1.27 (1.03−1.56)	0.13 (0.10−0.17)	177	1.17 (0.92−1.49)	0.17 (0.12−0.23)
Month 12	Aliskiren	200	0.23 (0.19−0.30)		124	0.22 (0.17−0.29)	
	Placebo	170	1.40 (1.10−1.80)	0.17 (0.12−0.23)	133	1.16 (0.89−1.52)	0.19 (0.13−0.27)
Plasma troponin I (ng/mL)							
Month 1	Aliskiren	387	0.66 (0.61−0.72)		253	0.75 (0.67−0.84)	
	Placebo	367	0.77 (0.70−0.84)	0.86 (0.77−0.97)	262	0.90 (0.80−1.00)	0.84 (0.72−0.97)
Month 6	Aliskiren	335	0.64 (0.58−0.71)		208	0.67 (0.60−0.76)	
	Placebo	306	0.76 (0.68−0.84)	0.84 (0.73−0.96)	209	0.75 (0.67−0.84)	0.90 (0.77−1.05)
Month 12	Aliskiren	262	0.65 (0.58−0.73)		158	0.69 (0.60−0.79)	
	Placebo	224	0.77 (0.68−0.87)	0.85 (0.73−0.99)	174	0.81 (0.71−0.92)	0.85 (0.71−1.02)
Plasma aldosterone (pmol/L)							
Month 1	Aliskiren	145	1.08 (0.93−1.26)		122	1.13 (0.96−1.34)	
	Placebo	140	1.69 (1.44−1.98)	0.64 (0.52−0.78)	118	1.49 (1.25−1.77)	0.76 (0.61−0.95)
Month 6	Aliskiren	130	1.00 (0.84−1.19)		98	1.53 (1.28−1.82)	
	Placebo	122	1.64 (1.37−1.97)	0.61 (0.48−0.76)	91	1.53 (1.28−1.83)	1.00 (0.79−1.25)
Month 12	Aliskiren	106	1.28 (1.05−1.57)		72	1.38 (1.12−1.71)	
	Placebo	89	1.85 (1.49−2.29)	0.69 (0.52−0.92)	76	1.64 (1.32−2.03)	0.84 (0.64−1.12)

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

with the established chronic HF paradigm that incremental increases in RAAS blockade with ACE inhibitors, ARB, and MRA improve patient outcomes.[13−16] In patients without DM, simultaneous use of aliskiren with other established RAAS therapies may maximize RAAS suppression and produce further clinical benefits.

In aggregate, the results of the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Disease Endpoints (ALTITUDE) and ASTRO-NAUT do not support a role for aliskiren in HHF patients already receiving an ACE inhibitor or ARB, particularly in those with comorbid DM. However, the potential benefits of aliskiren in non-diabetics should not be overlooked. Although outcomes in chronic ambulatory

HF have improved in recent decades, treatment and outcomes for patients admitted to the hospital for HF remain largely unchanged despite guideline recommended therapy.[17−19] Hospital admission for HF portends a poor prognosis and ASTRONAUT confirmed an unacceptably high post-discharge event rate among clinically and haemodynamically stable hospitalized patients.[6,20] Novel therapeutics are urgently needed and our data generate the hypothesis that aliskiren is safe, effective, and associated with a favourable neurohormonal profile in non-diabetic patients. Further insights may come from the ongoing long-term Aliskiren Trial on Minimizing Outcomes in Patients with Heart Failure (ATMOSPHERE).[21] In that study, analyses by
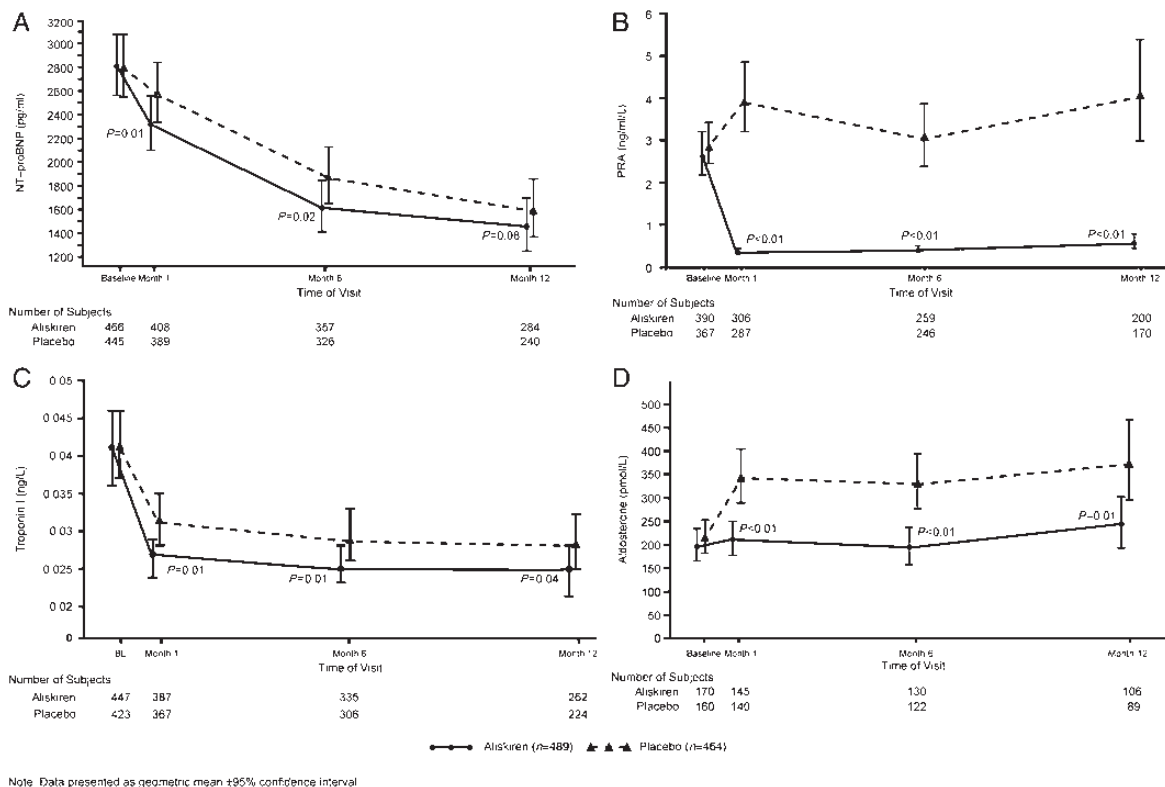
Figure 3 Measures of serum biomarkers (mean ± 95% confidence interval) at baseline and 1, 6, and 12 months post-randomization for non-diabetic patients receiving aliskiren and placebo. *P* values represent comparison between treatment arms of the change from baseline for a given biomarker. The figure reflects all available data for each biomarker at each time point. For NT-proBNP, note that the number of subjects for each time point differs slightly from the number of subjects reported in the repeated measure analysis displayed in *Table 4*. NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRA, plasma renin activity.

baseline DM status have again been pre-specified and may further define the risks and benefits of aliskiren in diabetic and non-diabetic patients.

The aforementioned features inherent to subgroup analyses constitute the major limitations of this work and these results must be considered hypothesis generating only. An additional limitation is the definition of DM used. The presence or absence of underlying DM was determined solely by the investigator and it was not mandatory to use objective criteria such as baseline use of diabetic medications or previous haemoglobin A1c values. Thus, it is possible that the DM status reported in ASTRONAUT may not perfectly overlap with the true biological DM status of this population.

Conclusions

In the pre-specified subgroup of ASTRONAUT patients with and without DM, the addition of aliskiren to standard therapy in non-diabetics appeared to improve post-discharge outcomes and biomarker profile, and was generally well-tolerated. In contrast, diabetic patients receiving aliskiren appeared to have worse post-discharge outcomes. Given the persistently high post-discharge event rate despite available therapies, future prospective investigations are

encouraged to confirm potential benefits of renin inhibition in a large cohort of HHF patients without DM.

Conflict of interest: A.P.M. has served on committees of clinical studies sponsored by Amgen, Bayer, Abbott Vascular, Cardiorentis, Johnson & Johnson, and Novartis Pharma AG. S.J.G. has no disclosures to report. G.C.F. has received grants from GlaxoSmithKline, the National Institutes of Health, and the Agency for Healthcare Research and Quality; served on speakers' bureaus for Boston Scientific/Guidant, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, and St Jude Medical; served as a consultant for Amgen, Gambro, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, Relypsa, Sdos, St Jude Medical, Medicines Company, Johnson & Johnson, and Takeda. M.B. has served as a consultant for Astra-Zeneca, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, AWD Dresden,

Table 5 Adverse events of special interest by treatment group among non-diabetics and diabetics (safety set)

	Aliskiren, n (%) Non-DM (n = 489) DM (n = 319)	Placebo, n (%) Non-DM (n = 465) DM (n = 345)	Aliskiren vs. Placebo relative risk (95% CI)	P for interaction (two-sided)
Adverse event of special interest				
Hyperkalaemia[a]				
Non-DM	96 (19.6)	74 (15.9)	1.23 (0.94–1.62)	
DM	73 (22.9)	68 (19.7)	1.16 (0.87–1.56)	0.80
Renal impairment or renal failure[b]				
Non-DM	75 (15.3)	48 (10.3)	1.49 (1.06–2.09)	
DM	59 (18.5)	50 (14.5)	1.28 (0.90–1.80)	0.57
Hypotension[c]				
Non-DM	88 (18.0)	56 (12.0)	1.49 (1.10–2.04)	
DM	50 (15.7)	46 (13.3)	1.18 (0.81–1.70)	0.33
Rate of treatment discontinuation due to adverse events				
Hyperkalaemia[a]				
Non-DM	16 (3.3)	10 (2.2)	1.52 (0.70–3.32)	
DM	20 (6.3)	13 (3.8)	1.66 (0.84–3.29)	0.85
Renal impairment or renal failure[b]				
Non-DM	19 (3.9)	9 (1.9)	2.01 (0.92–4.39)	
DM	13 (4.1)	12 (3.5)	1.17 (0.54–2.53)	0.34
Hypotension[c]				
Non-DM	18 (3.7)	9 (1.9)	1.90 (0.86–4.19)	
DM	11 (3.5)	10 (2.9)	1.19 (0.51–2.76)	0.43
Maximum or minimum post-baseline values				
Potassium ≥ 6 (mmol/L)				
Non-DM	32 (6.5)	26 (5.6)	1.17 (0.71–1.93)	
DM	31 (9.7)	14 (4.1)	2.39 (1.30–4.42)	0.07
eGFR <30 (mL/min/1.73 m^2)				
Non-DM	46 (9.4)	42 (9.0)	1.04 (0.70–1.55)	
DM	38 (11.9)	29 (8.4)	1.42 (0.90–2.24)	0.32

[a]Hyperkalaemia and increased blood potassium level.
[b]Abnormal renal function test, acute renal failure, decreased urine output, increased blood creatinine, acute pre-renal failure, renal impairment, renal failure, decreased glomerular filtration rate, and increased blood urea.
[c]Decreased blood pressure, postural dizziness, hypotension, orthostatic hypotension, and procedural hypotension.
CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

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