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Neurohumoral effects of aliskiren in patients with symptomatic heart failure receiving a mineralocorticoid receptor antagonist: the Aliskiren Observation of Heart Failure Treatment study

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Aims We evaluated the influence of concomitant mineralocorticoid receptor antagonists (MRAs) on the safety and neurohumoral effects of a direct renin inhibitor in the ALiskiren Observation of Heart Failure Treatment (ALOFT) study.

Methods and results Patients with stable New York Heart Association class II–IV heart failure (HF), plasma B-type natriuretic peptide (BNP) concentration >100 pg/mL, and treated with an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) and β-blocker were randomized to once-daily, double-blind treatment with aliskiren 150 mg or placebo, added to optimal HF therapy, for 12 weeks. Safety, tolerability, and effects of aliskiren on neurohumoral biomarkers were assessed in patients who received (MRA+) and did not receive (MRA−) MRA treatment at baseline. Of the 302 randomized patients, 101 were receiving MRA treatment (aliskiren, $n = 52$; placebo, $n = 49$). Mineralocorticoid receptor antagonist status did not affect the ability of aliskiren 150 mg, added to standard HF therapy, to lower BNP, N-terminal proBNP, plasma renin activity, and urinary aldosterone. For example, the end-of-study to baseline ratio of geometric mean for BNP was: MRA+ group: aliskiren 0.68 [95% confidence interval (CI) 0.47, 0.98], placebo 0.85 (0.58, 1.24); MRA− group: aliskiren 0.62 (0.45, 0.84), placebo 0.85 (0.63, 1.15), interaction $P = 0.720$. The incidence of pre-specified adverse events (renal dysfunction, symptomatic hypotension, and hyperkalaemia) was low, and there were no significant differences between aliskiren and placebo in either MRA subgroup.

Conclusion Aliskiren 150 mg added to standard HF therapy was well tolerated over 12 weeks and provided beneficial changes in neurohumoral biomarkers regardless of concomitant MRA treatment.

Keywords Aliskiren • B-type natriuretic peptide • Mineralocorticoid receptor antagonist • Renin

Introduction

The ALiskiren Observation of Heart Failure Treatment (ALOFT) study was a randomized, placebo-controlled study in 302 patients with symptomatic heart failure (HF). The study assessed the safety and neurohumoral effects of adding the direct renin inhibitor (DRI) aliskiren 150 mg once daily to standard therapy including an angiotensin-converting enzyme (ACE) inhibitor [or angiotensin receptor blocker (ARB), but not both] and a β-blocker.[1] ALOFT showed that aliskiren was effective in reducing levels of plasma

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B-type natriuretic peptide (BNP) and plasma N-terminal prohormone BNP (NT-proBNP), and was generally well tolerated over a 12-week period. Approximately one-third of patients in ALOFT were receiving a mineralocorticoid receptor antagonist (MRA) at baseline before being randomized to receive aliskiren or placebo, and could therefore have received combination treatment with three agents acting on the renin–angiotensin–aldosterone system (RAAS), i.e. an ACE inhibitor or ARB, MRA, and DRI (or even four agents if the renin-suppressing action of β-blockers is considered). The use of MRAs is likely to increase as a result of the findings of the recently reported Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) study.[2,3] In view of this and the concern about the safety of using multiple RAAS inhibitors,[4,5] a *post-hoc* subgroup analysis of ALOFT was undertaken to provide further insight into the potential efficacy and safety of adding aliskiren to the regimen of patients already receiving multiple RAAS inhibitors. This analysis is particularly relevant in the light of a major ongoing mortality and morbidity trial, Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) in which aliskiren is being added to conventional therapy, including, if the investigator chooses, an MRA.[6]

Methods

This was a *post-hoc* subgroup analysis of data from the ALOFT trial, a multicentre, randomized, double-blind, placebo-controlled study in patients with symptomatic HF that has been described in detail elsewhere.[1] This subgroup analysis evaluated patients according to whether they had or had not received an MRA as part of their standard HF therapy at baseline (MRA+ and MRA− subgroups, respectively). The study was performed in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki, and approved by the local and central ethical review boards, and all patients provided written informed consent.

Patients

Men and women aged ≥18 years with stable HF (New York Heart Association classes II–IV), a current or past diagnosis of hypertension, plasma BNP concentration >100 pg/mL (>28.9 pmol/L), and receiving a stable dose of an ACE inhibitor (or ARB) and a β-blocker (unless contraindicated or not tolerated) were eligible for inclusion. Patients receiving an ACE inhibitor in combination with an ARB were excluded from the study. Other key exclusion criteria included: HF related to obstructive valve disease or hypertrophic, restrictive, or infective cardiomyopathy; pregnancy; lung disease; systolic blood pressure <90 mmHg; and myocardial infarction, cerebrovascular accident, transient ischaemic attack, or coronary revascularization within 6 months of initiating screening.

Study design and assessments

Following a 2-week, single-blind, placebo run-in period to establish eligibility, patients were randomized equally to receive once-daily treatment with either aliskiren 150 mg or placebo for 12 weeks, in addition to their current HF therapy. Randomization was stratified according to left ventricular ejection fraction (LVEF) at baseline (LVEF >40% and ≤40%), and patients were evaluated at baseline and 12 weeks after randomization.

The primary objective of this study was to evaluate the safety and tolerability of aliskiren, specifically the incidence of the pre-defined adverse events of renal dysfunction [elevation of serum creatinine levels to >3.0 mg/dL (>265 μmol/L) or other adverse events related to renal dysfunction], hyperkalaemia (serum potassium levels >5.5 mmol/L or other adverse events related to hyperkalaemia) and symptomatic hypotension.

Efficacy endpoints included changes from baseline to the end of the study in levels of plasma NT-proBNP and other neurohumoral biomarkers, such as plasma BNP, plasma renin activity (PRA), plasma renin concentration (PRC) and urinary aldosterone, and mean sitting systolic and diastolic blood pressure (msSBP and msDBP). Echocardiograms were performed at the screening and Week 12 assessments, and were used to evaluate changes in cardiac size and left ventricular function.

Plasma renin activity was measured by means of radioimmunoassay of generated angiotensin I (DiaSorin kit; DiaSorin, Stillwater, MN, USA), of which the lower limit of quantification (LLOQ) was 0.2 ng/mL/h. Plasma renin concentration was measured by immunoradiometry using a solid-phase sandwich assay (Renin III Generation, CIS Bio International, Gif-sur-Yvette, France; LLOQ 1.0 pg/mL), as described initially by Ménard and co-workers and subsequently modified by Nussberger and colleagues. Plasma BNP concentration was measured using a two-site dual-monoclonal immunochemiluminescent assay (ADVIA Centaur BNP assay, Siemens Centaur XP, Malvern, PA, USA, Diagnostics Division). Plasma NT-proBNP concentration was measured using a chemiluminescent immunometric assay (Roche Diagnostics NT-proBNP Assay on ELECSYS 2010, Indianapolis, IN, USA). Total urinary aldosterone level was measured by radioimmunoassay (Siemens, Deerfield, IL, USA) following acidification with 3.2 N HCl and incubation for 24 h at room temperature in the dark.

All biomarkers were measured at Clinical Research Laboratories, Medinet in Breda, the Netherlands, or Lenexa, KS, USA. The coefficients of variation for the assays were as follows: PRA—17.1% at 0.20 ng/mL/h to 5.3% at 8.83 ng/mL/h; PRC—9.24% at 4.49 pg/mL to 7.22% at 43.29 pg/mL; BNP—5.85% at 39.2 pg/mL to 3.95% at 1535 pg/mL; NT-proBNP—3.6% at 131 pg/mL to 3.1% at 4259 pg/mL; urine aldosterone—7.2% at 15.8 μg/L to 5.5% at 78.5 μg/L.

Statistical analysis

Baseline parameters were compared for differences between treatment groups within the MRA+ and MRA− subgroups, using the *t*-test statistic for continuous characteristics and the χ^2 statistic (Fisher's exact test when any particular expected count was ≤5) for categorical characteristics. Between-treatment comparisons using least-squares means were performed for aliskiren vs. placebo in the overall population and within each of the MRA+ and MRA− subgroups. In order to perform the subgroup analysis, changes from baseline to endpoint (Week 12) were analysed using an analysis of covariance (ANCOVA) model with treatment, region, LVEF (>40 or ≤40%) and subgroup as factors, baseline as a covariate and treatment by subgroup as an interaction. A log-transformation was applied before analysis of the neurohumoral parameters (NT-proBNP, BNP, PRA, PRC, and urinary aldosterone). Treatment comparisons for the primary safety parameters, and the incidence of adverse events and laboratory abnormalities within each subgroup were analysed using Fisher's exact test or the χ^2 test. All statistical analyses were performed using SAS version 8.2 (or higher).

Table 1 Baseline demographic, clinical, and disease characteristics (intent-to-treat population)

	Overall population		Not MRA treated (MRA−)		MRA treated (MRA+)	
	Placebo ($n = 146$)	Aliskiren 150 mg ($n = 156$)	Placebo ($n = 97$)	Aliskiren 150 mg ($n = 104$)	Placebo ($n = 49$)	Aliskiren 150 mg ($n = 52$)
Demographic characteristics						
Age, year	68.4 ± 10.2	67.4 ± 10.6	70.2 ± 9.8	68.4 ± 10.4	64.9 ± 10.2	65.3 ± 10.8
Male, *n* (%)	111 (76.0)	125 (80.1)	81 (83.5)	84 (80.8)	30 (61.2)	41 (78.8)
Caucasian, *n* (%)	144 (98.6)	150 (96.2)	97 (100)	101 (97.1)	47 (95.9)	49 (94.2)
Clinical characteristics						
eGFR, mL/min/1.73 m^2	67.8 ± 19.1	70.0 ± 21.3	68.4 ± 20.7	69.2 ± 20.5	66.4 ± 15.8	71.7 ± 22.9
BMI ≥ 30 kg/m^2, *n* (%)	33 (22.6)	42 (26.9)	19 (19.6)	25 (24.0)	14 (28.6)	17 (32.7)
Disease characteristics						
Heart failure						
Time since diagnosis, years	4.9 ± 5.3	4.1 ± 3.9	4.7 ± 5.7	3.9 ± 3.7	5.1 ± 4.6	4.3 ± 4.3
Aetiology, *n* (%)						
Ischaemic	79 (54.1)	86 (55.1)	56 (57.7)	61 (58.7)	23 (46.9)	25 (48.1)
Idiopathic cardiomyopathy	29 (19.9)	36 (23.1)	18 (18.6)	25 (24.0)	11 (22.4)	11 (21.2)
Hypertensive	25 (17.1)	25 (16.0)	18 (18.6)	15 (14.4)	7 (14.3)	10 (19.2)
Other	13 (8.9)	9 (5.8)	5 (5.2)	3 (2.9)	8 (16.3)	6 (11.5)
LVEF ≤40%, *n* (%)[a]	122 (92.4)	132 (95.0)	77 (79.4)	90 (86.5)	45 (91.8)	42 (80.8)
NYHA class, *n* (%)						
I	1 (0.7)	0	1 (1.0)	0	0	0
II	87 (59.6)	98 (62.8)	58 (59.8)	69 (66.3)	29 (59.2)	29 (55.8)
III	58 (39.7)	56 (35.9)	38 (39.2)	34 (32.7)	20 (40.8)	22 (42.3)
IV	0	2 (1.3)	0	1 (1.0)	0	1 (1.9)
Duration of hypertension, years	12.3 ± 9.6	11.4 ± 8.7	12.8 ± 10.2	10.5 ± 8.6	11.2 ± 8.4	13.3 ± 8.7
Diabetes, *n* (%)	49 (33.6)	57 (36.5)	36 (37.1)	38 (36.5)	13 (26.5)	19 (36.5)
Concomitant medication						
ACE inhibitor, *n* (%)	123 (84.2)	130 (83.3)	77 (79.4)	85 (81.7)	46 (93.9)	45 (86.5)
ARB, *n* (%)	21 (14.4)	25 (16.0)	18 (18.6)	19 (18.3)	3 (6.1)	6 (11.5)
β-blocker, *n* (%)	138 (94.5)	147 (94.2)	92 (94.8)	96 (92.3)	46 (93.9)	51 (98.1)

All values are mean ± SD unless otherwise stated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.
[a]As measured by core echocardiography laboratory.

Results

Following the 2-week placebo run-in period, 302 patients were randomized to once-daily treatment for 12 weeks with aliskiren 150 mg ($n = 156$) or placebo ($n = 146$), in addition to standard therapy for HF (ACE inhibitor or ARB, plus β-blocker). In total, 277 patients (91.7%) completed the double-blind treatment phase. A total of 101 patients (aliskiren, $n = 52$; placebo, $n = 49$) were receiving MRA treatment at baseline as part of their background HF therapy.

Baseline patient characteristics

Patient characteristics were generally well matched between the aliskiren and placebo treatment arms within each of the MRA− and MRA+ subgroups (*Table 1*). Patients in the MRA+ subgroup tended to be younger than patients in the MRA− subgroup (mean age of 65 vs. 69 years, respectively) and a greater proportion of them (31 vs. 22%, respectively) were obese [body mass index (BMI) ≥30 kg/m^2]. There was a lower proportion of men (70 vs. 82%) and a lower proportion of patients with ischaemic heart disease (48 vs. 58%) in the MRA+ subgroup than in the MRA− subgroup, respectively. The proportion of patients receiving an ACE inhibitor was slightly higher in the MRA+ subgroup than in the MRA− subgroup (90 vs. 81%, respectively). The most commonly used ACE inhibitors were ramipril ($n = 88$), enalapril ($n = 60$), lisinopril ($n = 33$), and perindopril ($n = 28$). The median daily doses in the aliskiren and placebo groups, respectively, were ramipril (5 vs. 5 mg), enalapril (20 vs. 10 mg), lisinopril (20 vs.

Table 2 Baseline neurohumoral and echocardiographic parameters (intent-to-treat population)

	Overall population		Not MRA treated (MRA−)		MRA treated (MRA+)	
	Placebo (*N* = 146)	Aliskiren 150 mg (*N* = 156)	Placebo (*N* = 97)	Aliskiren 150 mg (*N* = 104)	Placebo (*N* = 49)	Aliskiren 150 mg (*N* = 52)
Neurohumoral parameters						
Plasma BNP, pg/mL	[*n* = 145]	[*n* = 154]	[*n* = 96]	[*n* = 102]	[*n* = 49]	[*n* = 52]
	191.5	204.8	182.4	194.9	210.9	225.6
	(165.2, 222.1)	(175.0, 239.6)	(149.8, 222.0)	(160.1, 237.2)	(168.8, 263.5)	(171.5, 296.8)
Plasma NT-proBNP, pg/mL	[*n* = 141]	[*n* = 147]	[*n* = 93]	[*n* = 95]	[*n* = 48]	[*n* = 52]
	1217	1387	1125	1244	1417	1690
	(1002, 1479)	(1168, 1647)	(870, 1457)	(998, 1551)	(1055, 1903)	(1275, 2240)
PRA, ng/mL/h	[*n* = 138]	[*n* = 146]	[*n* = 94]	[*n* = 96]	[*n* = 44]	[*n* = 50]
	2.2 (1.7, 3.0)	1.8 (1.3, 2.4)	1.8 (1.2, 2.6)	1.4 (1.0, 2.1)	3.8 (2.3, 6.2)	2.8 (1.6, 4.8)
PRC, ng/L	[*n* = 134]	[*n* = 144]	[*n* = 93]	[*n* = 94]	[*n* = 41]	[*n* = 50]
	30.8	25.2	25.6	21.0	46.5	35.7
	(24.2, 39.1)	(19.9, 32.0)	(19.0, 34.5)	(16.0, 27.5)	(30.9, 70.2)	(22.5, 56.8)
Urinary aldosterone, nmol/day	[*n* = 131]	[*n* = 145]	[*n* = 89]	[*n* = 97]	[*n* = 42]	[*n* = 48]
	22.7	24.3	22.3	23.0	23.7	27.1
	(19.0, 27.1)	(20.8, 28.4)	(18.0, 27.6)	(18.9, 28.0)	(16.9, 33.3)	(20.7, 35.6)
Echocardiographic parameters						
MR/LA, %	[*n* = 97]	[*n* = 101]	[*n* = 63]	[*n* = 66]	[*n* = 34]	[*n* = 35]
	29.5 ± 13.1	30.2 ± 13.8	29.3 ± 13.2	29.7 ± 12.3	29.9 ± 13.1	31.1 ± 16.5
LVEF, %[a]	[*n* = 132]	[*n* = 139]	[*n* = 85]	[*n* = 95]	[*n* = 47]	[*n* = 44]
	31.1 ± 5.5	30.6 ± 5.5	31.9 ± 5.3	31.0 ± 5.3	29.6 ± 5.4	29.6 ± 5.8
Blood pressure	[*n* = 146]	[*n* = 156]	[*n* = 97]	[*n* = 104]	[*n* = 49]	[*n* = 52]
msSBP, mmHg	127.6 ± 16.4	130.2 ± 18.3	128.8 ± 16.5	133.0 ± 17.2	125.1 ± 16.1	124.7 ± 19.2
msDBP, mmHg	76.4 ± 8.4	78.1 ± 10.4	77.1 ± 8.4	78.5 ± 10.0	75.1 ± 8.5	77.1 ± 11.3

Neurohumoral parameters are shown as geometric mean (95% confidence interval). Echocardiographic parameters are shown as mean ± SD. Data for patients with a value at baseline are included.

BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MR/LA, mitral regurgitation to left atrial area ratio; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PRA, plasma renin activity; PRC, plasma renin concentration.

[a]As measured by core echocardiography laboratory.

12.5 mg), and perindopril (4 vs. 2 mg). In the aliskiren group at baseline, 8 patients were treated with potassium canrenoate 25 mg daily; 2 with eplerenone 25 mg, and 1 with 50 mg daily; 5 with spironolactone 12.5 mg, 23 with 25 mg, 1 with 37.5 mg, 11 with 50 mg, and 2 with 100 mg daily. In the placebo group, 4 patients were treated with potassium canrenoate 25 mg, 6 with 50 mg, and 1 with 125 mg daily; none with eplerenone and 2 with spironolactone 12.5 mg, 26 with 25 mg, 9 with 50 mg, and 1 with 100 mg daily.

Baseline neurohumoral and echocardiographic parameters were also well matched between aliskiren and placebo treatment arms within each MRA subgroup (*Table 2*). Patients in the MRA+ subgroup had higher geometric mean baseline PRA (aliskiren 2.8, placebo 3.8 ng/mL/h) and PRC (aliskiren 35.7, placebo 46.5 ng/L) than those in the MRA− subgroup (PRA: aliskiren 1.4, placebo 1.8 ng/mL/h; PRC: aliskiren 21.0, placebo 25.6 ng/L).

Changes in neurohumoral parameters

In the overall population, aliskiren 150 mg added to standard HF therapy significantly reduced geometric mean BNP (36%), NT-proBNP (27%), PRA (82%), and urinary aldosterone (19%) levels compared with placebo, and significantly increased PRC (161%) (*Figure 1A–E*). Changes in neurohumoral parameters with aliskiren compared with placebo were similar in the MRA+ and MRA− subgroups; ANCOVA revealed no significant interaction between MRA treatment and the effect of aliskiren for any neurohumoral parameter (*Figure 3A*). Although there were modest differences in geometric mean reductions with aliskiren relative to placebo in plasma NT-proBNP in the MRA+ subgroup relative to the MRA− subgroup, these may be attributed to differences in baseline levels; 95% confidence intervals for the two subgroups were completely overlapping and there was no significant interaction with MRA treatment status (*Figure 3A*).

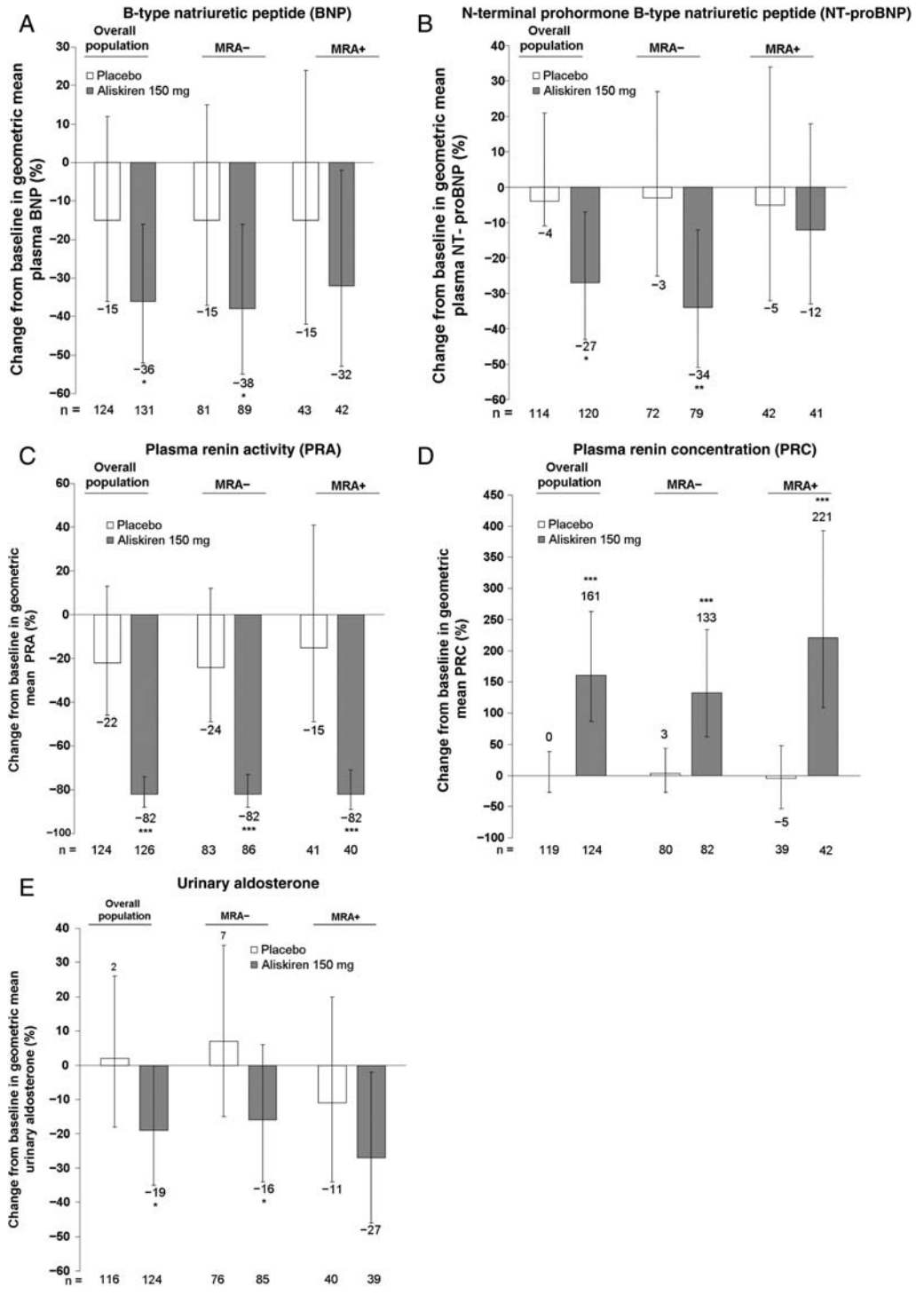

Figure 1 Changes from baseline in neurohumoral biomarkers according to mineralocorticoid receptor antagonist treatment status. (*A*) B-type natriuretic peptide, (*B*) N-terminal prohormone B-type natriuretic peptide, (*C*) plasma renin activity, (*D*) plasma renin concentration, and (*E*) urinary aldosterone. Data represent (*A*–*E*) percentage change from baseline in geometric mean (95% CI) in the overall population and the subgroups of patients receiving (MRA+) or not receiving (MRA−) MRA treatment during the study. *P* values were calculated using a two-way ANCOVA model with treatment, region, LVEF (>40 or ≤40%) and subgroup as factors, baseline as a covariate and treatment by subgroup as an interaction. *$P < 0.05$ vs. placebo; **$P < 0.005$ vs. placebo; ***$P < 0.0001$ vs. placebo. ANCOVA, analysis of covariance; CI, confidence interval; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

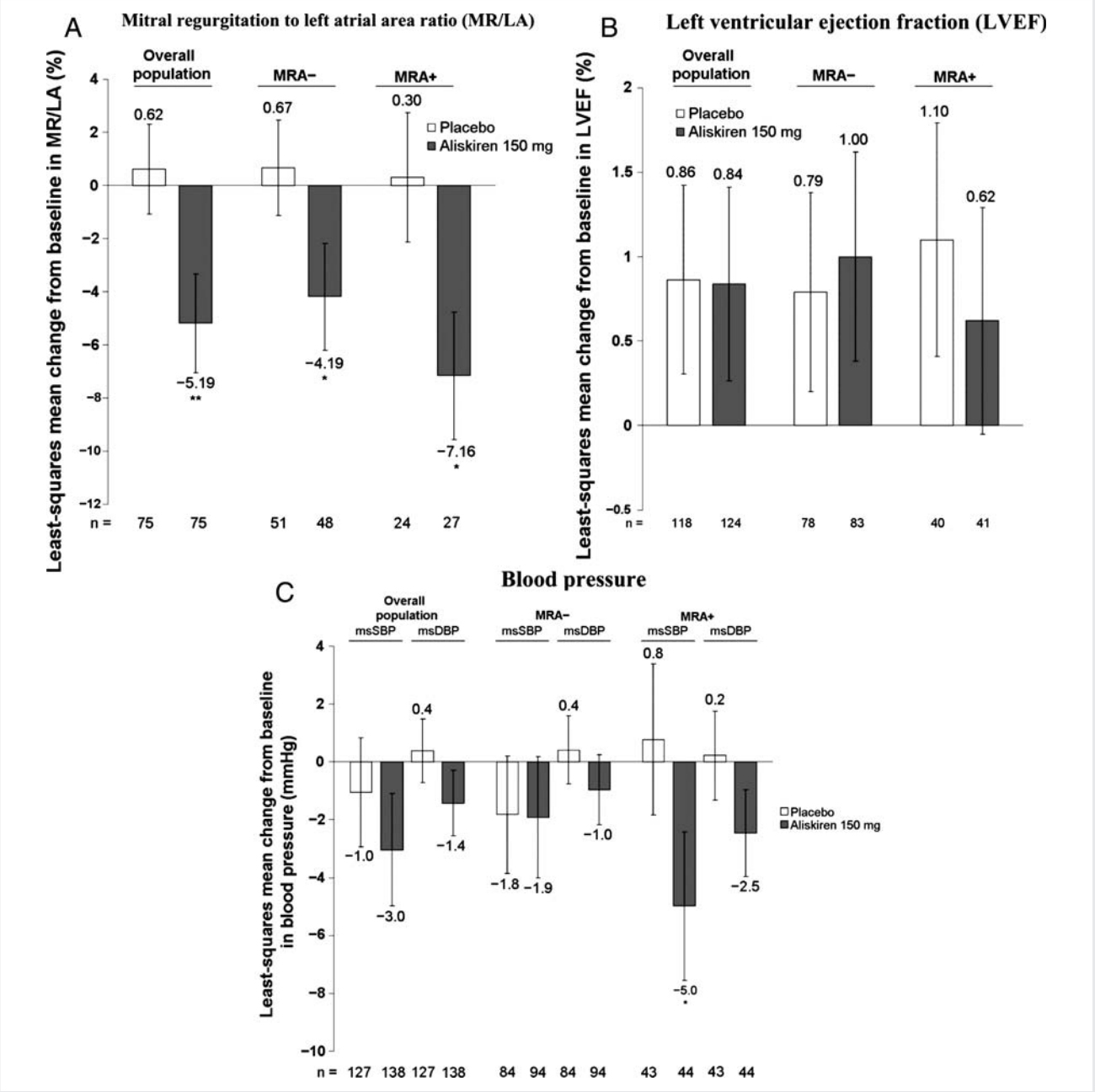

Figure 2 Changes from baseline in echocardiography parameters and blood pressure according to MRA treatment status. (*A*) Mitral regurgitation to left atrial area ratio, (*B*) LVEF, and (*C*) blood pressure. Data (*A*–*C*) represent least-squares mean ± SEM in the overall population and the subgroups of patients receiving (MRA+) or not receiving (MRA−) MRA treatment during the study. *P* values were calculated using a two-way ANCOVA model with treatment, region, LVEF (>40 or ≤40%) and subgroup as factors, baseline as a covariate and treatment by subgroup as an interaction. *$P < 0.05$ vs. placebo. ANCOVA, analysis of covariance; CI, confidence interval; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; SEM, standard error of the mean.

Changes in echocardiographic parameters

In the overall population, aliskiren 150 mg significantly improved the mitral regurgitation to left atrial area ratio (MR/LA) compared with placebo (−5.2 vs. +0.6%, $P = 0.0003$; *Figure 2A*); MRA treatment status did not influence this effect of aliskiren (interaction $P = 0.429$; *Figure 3B*). Aliskiren treatment was associated with small numerical increases in LVEF in the overall population and in the MRA− and MRA+ subgroups (*Figure 2B*), but these changes were not significantly different from those seen with placebo and there was no influence of MRA treatment status (interaction $P = 0.409$; *Figure 3B*).

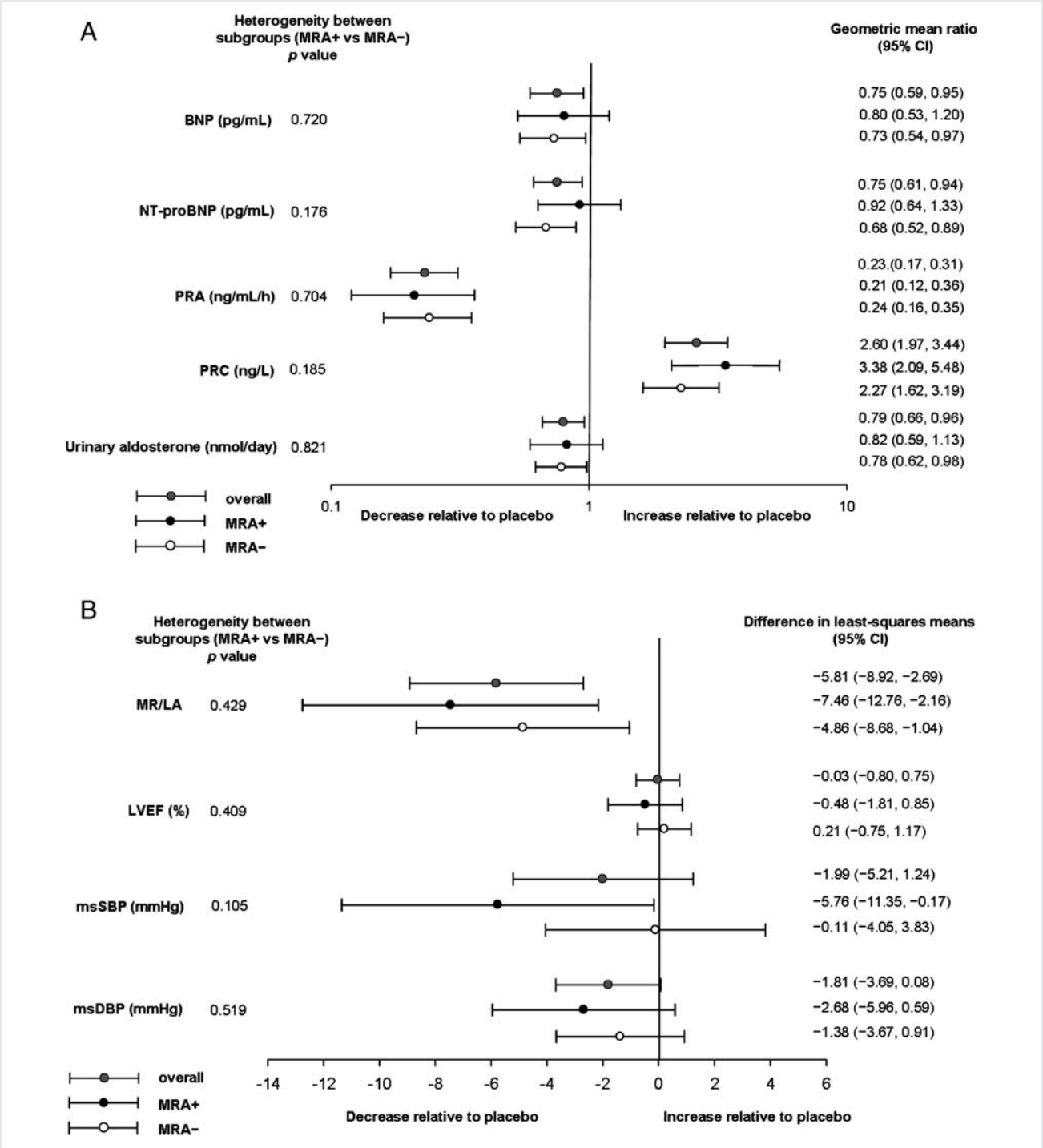

Figure 3 Influence of MRA treatment on between-treatment comparisons (aliskiren vs. placebo) in (*A*) neurohumoral biomarkers and (*B*) echocardiography parameters and blood pressure. Data are shown as ratio (aliskiren:placebo) of the geometric mean with associated 95% confidence intervals (BNP, NT-proBNP, PRA, PRC, urinary aldosterone) or least-squares mean difference (aliskiren − placebo) with associated 95% confidence intervals (MR/LA, LVEF, blood pressure). *P* values were calculated using an ANCOVA model with treatment, region, LVEF (>40 or $\leq 40\%$) and subgroup as factors, baseline as a covariate and treatment by subgroup as an interaction. ANCOVA, analysis of covariance; BNP, B-type natriuretic peptide; CI, confidence interval; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MR/LA, mitral regurgitation to left atrial area ratio; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PRA, plasma renin activity; PRC, plasma renin concentration.

Table 3 Safety and tolerability (intent-to-treat population)

Pre-specified adverse event	Overall population			Not MRA treated (MRA−)			MRA treated (MRA+)		
	Placebo (*N* = 146)	Aliskiren 150 mg (*N* = 156)	*P*-value	Placebo (*N* = 97)	Aliskiren 150 mg (*n* = 104)	*P*-value	Placebo (*n* = 49)	Aliskiren 150 mg (*n* = 52)	*P*-value
Any event of renal dysfunction, symptomatic hypotension, or hyperkalaemia	11 (7.5)	17 (10.9)	0.329	7 (7.2)	8 (7.7)	0.898	4 (8.2)	9 (17.3)	0.170
Renal dysfunction	2 (1.4)	3 (1.9)	1.000	2 (2.1)	1 (1.0)	0.610	0	2 (3.8)	0.495
Symptomatic hypotension	2 (1.4)	5 (3.2)	0.450	1 (1.0)	2 (1.9)	1.000	1 (2.0)	3 (5.8)	0.618
Hyperkalaemia	7 (4.8)	10 (6.4)	0.499	4 (4.1)	5 (4.8)	1.000	3 (6.1)	5 (9.6)	0.716

Table shows the number (%) of patients experiencing a pre-specified adverse event.
MRA, mineralocorticoid receptor antagonist.

Table 4 Laboratory abnormalities (safety population)

Laboratory abnormalities	Overall population		Not MRA treated (MRA−)		MRA treated (MRA+)	
	Placebo (*N* = 146)	Aliskiren 150 mg (*N* = 156)	Placebo (*N* = 97)	Aliskiren 150 mg (*N* = 104)	Placebo (*N* = 49)	Aliskiren 150 mg (*N* = 52)
	[*n* = 144]	[*n* = 156]	[*n* = 96]	[*n* = 104]	[*n* = 48]	[*n* = 52]
Serum potassium						
<3.5 mmol/L	7 (4.9)	2 (1.3)	3 (3.1)	0	4 (8.3)	2 (3.8)
>5.5 mmol/L	12 (8.3)	13 (8.3)	7 (7.3)	6 (5.8)	5 (10.4)	7 (13.5)
≥6.0 mmol/L	6 (4.2)	3 (1.9)	4 (4.2)	2 (1.9)	2 (4.2)	1 (1.9)
Serum creatinine						
>177 μmol/L	8 (5.6)	11 (7.1)	6 (6.3)	8 (7.7)	2 (4.2)	3 (5.8)
>265 μmol/L	3 (2.1)	0	3 (3.1)	0	0	0
BUN						
>14.3 mmol/L	15 (10.4)	13 (8.3)	7 (7.3)	6 (5.8)	8 (16.7)	7 (13.5)

Table shows the number (%) of patients experiencing clinically notable changes in selected laboratory values while receiving treatment.
BUN, blood urea nitrogen; MRA, mineralocorticoid receptor antagonist.

Changes in blood pressure

In the overall population, there was no significant between-treatment difference in the change from baseline in msSBP or msDBP (*Figure 2C*). In the MRA+ subgroup, aliskiren treatment was associated with a significant decrease in msSBP (−5.0 vs. +0.8 mmHg, $P < 0.05$) from baseline compared with placebo (*Figure 2C*). Analysis of covariance revealed no significant interaction between MRA treatment status and the effect of aliskiren on msSBP (interaction $P = 0.105$; *Figure 3B*) or msDBP (interaction $P = 0.519$; *Figure 3B*).

Safety and tolerability

Addition of aliskiren to standard HF treatment was generally well tolerated. There were no significant differences between the aliskiren 150 mg and placebo treatment groups in the proportion of patients who experienced at least one pre-defined adverse event (renal dysfunction, symptomatic hypotension, or hyperkalaemia) in the overall population (*Table 3*). There were more adverse events with aliskiren compared with placebo in the MRA+ subgroup than in the MRA− one, although the numbers were small and the increase was not statistically significant (*Table 3*). There were also no notable differences between the aliskiren and placebo groups in the proportion of patients with elevations above pre-defined threshold in blood urea nitrogen, serum creatinine, or serum potassium levels in either the MRA+ or the MRA− subgroups (*Table 4*).

Discussion

Recently, the value of adding another blocker of the effects of angiotensin II to an ACE inhibitor in patients with HF has been

questioned while the indication for using an MRA has broadened to potentially all patients with systolic HF. Specifically, the interpretation of trials adding an ARB to an ACE inhibitor has become controversial. The risk of death from cardiovascular causes was not reduced in each of the two large placebo-controlled trials in HF (although the risk of HF hospitalization was in both).[7,8] Secondly, the background ACE inhibitor and dose did not match the evidence-based and regulatory standard (i.e. enalapril at an average daily dose of 16.6 mg). Doubt about the trials in HF has arisen because of the findings of two more recent ARB 'add-on' trials: one in patients with acute myocardial infarction and the other in patients with stable arterial disease.[9,10] In both, addition of an ARB to a full dose of an evidence-based ACE inhibitor had no clinical benefit. Furthermore, in all of the ARB 'add-on' trials, addition of an ARB to an ACE inhibitor led to increased rates of hypotension, renal dysfunction, and hyperkalaemia.[4,5]

More recently, an unequivocal benefit of an MRA has been shown in patients with systolic HF and mild symptoms, consistent with two other trials with an MRA in systolic HF with severe symptoms and systolic HF after acute myocardial infarction.[2,3,11,12] MRA were not commonly used at baseline in the aforementioned ARB trials. Consequently, both the efficacy and safety questions about adding a second renin–angiotensin blocker to an ACE inhibitor have changed. In terms of efficacy, it is now important to know whether the second renin–angiotensin blocker provides incremental benefit not only on top of a full dose of an evidence-based ACE inhibitor but also an MRA. This obviously raises a new safety question about adding a second renin–angiotensin blocker not only to an ACE inhibitor but also an MRA (and β-blocker).

The results of the current *post-hoc* analysis suggest that the efficacy of aliskiren is maintained in patients receiving an MRA (MRA+) at baseline, as evidenced by a similar reduction in plasma BNP and NT-proBNP to those in the MRA− subgroup. Consistent with the results for the overall population, the present analysis also showed that addition of aliskiren to standard HF therapy led to reductions in urinary aldosterone and PRA levels that were similar in both MRA subgroups. Most importantly, the addition of aliskiren to the MRA+ subset was generally well tolerated even though these patients were receiving three RAAS inhibitors (ACE inhibitor or ARB, MRA, and DRI), as well as a β-blocker in most cases. Specifically, addition of aliskiren to standard HF treatment with or without an MRA was not associated with an increased incidence of pre-specified adverse events including symptomatic hypotension, renal dysfunction, or hyperkalaemia. Although there was a reduction in systolic blood pressure when aliskiren was added to the MRA+ group, this reduction was not significantly different from that observed in the MRA− group. In addition, there were no significant differences between the aliskiren and placebo groups in the proportion of patients with an elevation of blood urea nitrogen, serum creatinine, or serum potassium levels.

Although reductions in the levels of plasma BNP and NT-proBNP have been associated with improved clinical outcomes in HF, these are only surrogate outcomes.[13–15] Additionally, a *post-hoc* analysis of one of the ARB 'add-on trials' showed that the benefit of candesartan was consistent irrespective of background use of an MRA.[16] Both surrogate outcomes and *post-hoc* analyses can be misleading.[17] Fortunately, the safety and efficacy of adding aliskiren to conventional therapy in patients with HF is being addressed, appropriately, in an ongoing, large-scale, mortality–morbidity trial (ATMOSPHERE) in which the renin inhibitor is being compared directly with enalapril 10 mg twice daily and also given in addition to enalapril 10 mg twice daily, i.e. a three-arm trial.[6]

In summary, this retrospective analysis of the ALOFT study showed that the natriuretic peptide lowering effect of aliskiren was consistent in patients not treated and treated with an MRA and that there was no excess of renal dysfunction when aliskiren was added to an ACE inhibitor (or ARB) and MRA, as well as a β-blocker in most cases. However, only the results of a well-powered, prospective, randomized trial will answer the question as to whether the addition of a DRI to an ACE inhibitor (or ARB) and a β-blocker with or without an MRA will be safe and effective in patients with HF.

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