Aliskiren-based therapy lowers blood pressure more effectively than hydrochlorothiazide-based therapy in obese patients with hypertension: sub-analysis of a 52-week, randomized, double-blind trial

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Objectives **To compare the long-term efficacy, safety and tolerability of the direct renin inhibitor aliskiren against the diuretic hydrochlorothiazide (HCTZ) in obese patients with hypertension.**

Methods **A *post hoc* analysis of 396 obese patients (body mass index $\geq$30 kg/m^2) in a 52-week study in 1124 patients with hypertension was performed. Patients were randomized to receive aliskiren 150 mg or HCTZ 12.5 mg for 3 weeks, or placebo for 6 weeks. At week 3, active treatment doses were doubled. Patients receiving placebo were randomized to aliskiren 300 mg or HCTZ 25 mg at week 6. Add-on amlodipine 5–10 mg was permitted from week 12 to achieve blood pressure (BP) control (<140/90 mmHg).**

Results **In the subgroup of obese patients, aliskiren monotherapy provided significantly greater BP reductions than HCTZ at week 12 endpoint (−16.7/−12.3 vs. −12.2/−9.1 mmHg, $P \leq 0.001$). Reductions were also greater with aliskiren-based therapy than HCTZ-based therapy at week 52 endpoint (−19.9/−15.5 vs. −17.5/−13.3 mmHg; $P = 0.138$ for systolic BP and $P = 0.007$ for diastolic BP). Mean BP reductions from baseline with aliskiren-based therapy were similar in obese and nonobese patients. By contrast, HCTZ-based therapy provided significantly smaller mean reductions in BP from baseline in obese patients vs. nonobese patients ($P < 0.05$). Aliskiren-based therapy was generally well tolerated in obese patients, and was associated with a significantly lower incidence of hypokalemia (1.0 vs. 14.0%, $P < 0.0001$) than HCTZ-based therapy.**

Conclusion **Aliskiren-based therapy provided superior BP reductions to HCTZ-based therapy with good tolerability in obese patients with hypertension. *J Hypertens* 27:1493–1501 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: aliskiren, amlodipine, antihypertensive therapy, calcium channel blocker, direct renin inhibitor, diuretic, hydrochlorothiazide, hypertension, obesity

Abbreviations: ACE, angiotensin-converting enzyme; AE, adverse event; ANCOVA, analysis of covariance; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; SAE, serious adverse event; SD, standard deviation

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Introduction

Approximately 75% of obese patients (BMI $\geq$ 30 kg/m^2) have hypertension, and yet fewer than 20% have their blood pressure (BP) controlled to below 140/90 mmHg [1]. Clearly, there is a need for new antihypertensive treatment options for these patients. Obesity-associated hypertension primarily involves activation of the renin system [2,3], volume expansion and increased cardiac output [4–6]; systemic vasoconstriction plays a lesser role. Guidelines for the treatment of hypertension do not include specific recommendations on drug therapy for obese patients with hypertension [7,8]. Furthermore, contradictory suggestions have been made as to what the first-line treatment in obese patients should be [9–11], with few studies directly addressing this issue [12].

Aliskiren is the first in a new class of oral direct renin inhibitors approved for the treatment of hypertension [13]. Aliskiren inhibits the action of renin on angiotensinogen, and so suppresses the renin system by targeting the system at its first and rate-limiting step [14]. Aliskiren provides highly effective BP-lowering across a broad range of patient populations, independent of age,

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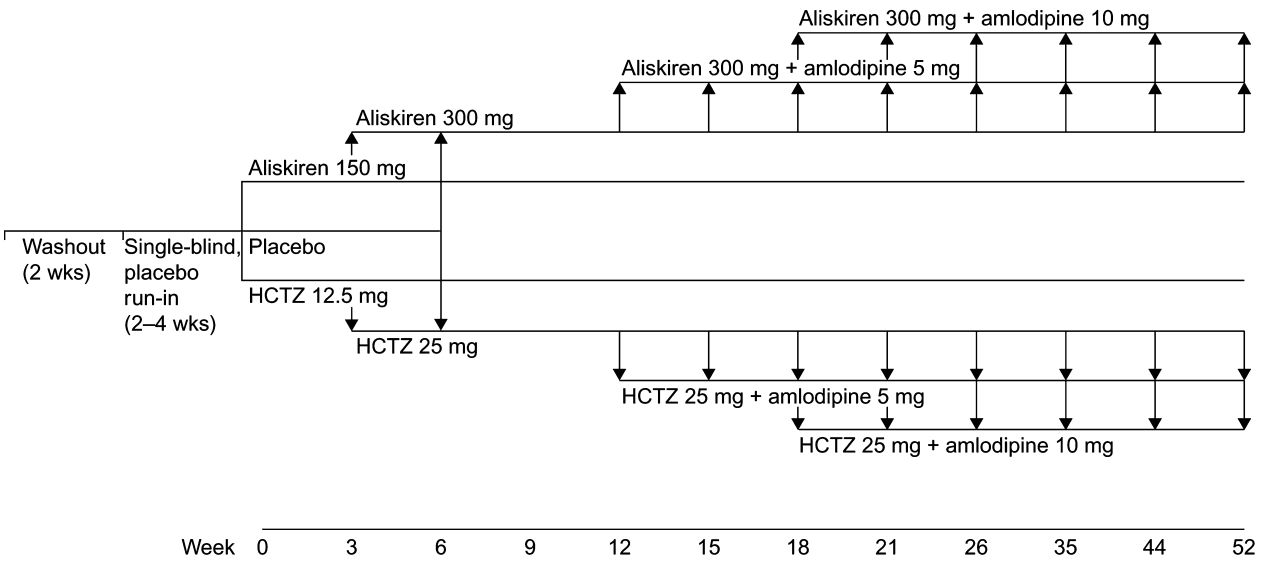
Fig. 1



Study design. From week 12, patients not achieving blood pressure <140/90 mmHg could receive add-on amlodipine 5 mg, titrated to 10 mg from week 18. HCTZ, hydrochlorothiazide.

sex and race [15], and a pooled analysis of 8481 patients with hypertension enrolled in aliskiren studies showed that aliskiren lowered BP equally effectively in obese and nonobese patients [16]. Moreover, a study of 560 obese patients with hypertension who were nonresponsive to hydrochlorothiazide (HCTZ) 25 mg monotherapy showed that combination therapy with aliskiren 300 mg and HCTZ 25 mg provided clinically significant additional BP reductions [17]. Indeed, significantly more patients with hypertension and class 3 obesity (BMI $\geq$40 kg/m^2) achieved BP control with aliskiren/HCTZ therapy than during combination therapy with HCTZ and the calcium channel blocker amlodipine [18].

We previously reported the results of a 52-week randomized, double-blind, active-controlled trial that evaluated the long-term efficacy, safety and tolerability of aliskiren-based therapy compared with HCTZ-based therapy in patients with hypertension [19]. The study showed that aliskiren-based treatment (monotherapy or with optional addition of amlodipine) provided significantly greater BP reductions than HCTZ-based treatment (monotherapy or with optional addition of amlodipine), and was well tolerated. Here, we report the results of a *post hoc* analysis of the BP-lowering efficacy and safety of aliskiren-based therapy vs. HCTZ-based therapy over 52 weeks in the subgroup of obese patients in this trial.

Patients and methods

Patients

This was a randomized, double-blind, parallel-group, multicenter trial. The study design (Fig. 1), and patient inclusion and exclusion criteria have been reported previously [19]. Briefly, eligible individuals were outpatients aged at least 18 years, with grade 1–2 hypertension [mean sitting diastolic blood pressure (msDBP) $\geq$90 mmHg and <110 mmHg] at the single-blind placebo run-in visit. At randomization, patients had to have msDBP at least 95 mmHg and less than 110 mmHg, and show a difference of 10 mmHg or less in msDBP compared with the value at their previous study visit. Patients with msDBP at least 110 mmHg and/or mean sitting systolic blood pressure (msSBP) at least 180 mmHg were excluded, as were patients with secondary hypertension, diabetes mellitus with poor glycemic control or microalbuminuria, history of severe cardiovascular or cerebrovascular disease, or other severe or life-threatening disease.

All patients provided written informed consent before undergoing any study procedure. The study protocol was approved by the appropriate local ethical review boards and was conducted in accordance with Good Clinical Practice and in compliance with the Declaration of Helsinki.

Study design

Following screening, patients entered a 2–4-week single-blind placebo run-in period to establish baseline BP (preceded by a 2-week wash-out period for patients taking antihypertensive treatment). All eligible patients were then randomized to receive once-daily treatment with aliskiren 150 mg, HCTZ 12.5 mg or placebo. After 3 weeks, patients receiving aliskiren 150 mg or HCTZ 12.5 mg underwent forced titration to aliskiren 300 mg or HCTZ 25 mg, respectively. After a further 3 weeks,

patients in the placebo group were reassigned to either aliskiren 300 mg or HCTZ 25 mg for 20 weeks. After this time, patients were entered into a 26-week extension period on the same treatment. For patients not achieving the target BP of less than 140/90 mmHg, addition of amlodipine 5 mg was permitted from week 12, with titration to 10 mg from week 18.

Study objectives

The primary objective of this study was to compare the long-term efficacy of an aliskiren-based treatment regimen with an HCTZ-based treatment regimen in patients with essential hypertension by testing noninferiority and superiority (if noninferiority was established) of aliskiren-based therapy vs. HCTZ-based therapy. The primary efficacy variable was the change from baseline in msDBP. The results of this analysis have been reported previously [19].

Here we report the results of a *post hoc* analysis of the changes from baseline in msSBP and msDBP, rates of BP response (msDBP <90 mmHg or decrease from baseline ≥10 mmHg) and BP control (BP <140/90 mmHg), and safety and tolerability of study treatments at week 12 and week 52 endpoints in the subgroup of obese patients (BMI ≥30 kg/m^2; $n = 396$) compared with nonobese patients (BMI <30 kg/m^2, $n = 721$).

Blood pressure measurements

Clinic BP was measured at baseline and at weeks 3, 6, 9, 12, 15, 18, 21, 26, 35, 44 and 52 using a mercury sphygmomanometer. Sitting BP was measured at trough (24 ± 3 h postdose) in the arm in which the msDBP was highest at the first study visit. After the patient had been sitting for 5 min, three sitting BP measurements were taken at 1–2-min intervals; the value for the visit was recorded as the mean of these.

Safety and tolerability assessments

Safety and tolerability assessments included the regular monitoring and recording of all adverse events, vital signs, laboratory test results (hematology, blood chemistry and urinalysis) and physical examinations. The safety population comprises all randomized patients who had received at least one dose of the study drug and had at least one postbaseline safety assessment. Adverse events were assessed for the obese and nonobese subgroups, as well as for the overall safety population.

Statistical analyses

Statistical methods and the results of the primary efficacy analysis have been reported previously [19]. In the *post hoc* analysis, least-squares mean changes from baseline in msSBP and msDBP at week 12 and week 52 endpoints were analyzed for the subgroups of patients [intent-to-treat (ITT) population] who were obese or nonobese at baseline, and who were obese and aged less than 65 years or at least 65 years at baseline, using a one-way analysis of covariance (ANCOVA) model with treatment as covariate. BP response and control rates at week 12 and week 52 endpoints, rates of adverse events, and laboratory abnormalities were compared using either a chi-squared or Fisher's exact test. Week 12 endpoint and week 52 endpoint data were the values at week 12 or week 52, or the last postbaseline value collected prior to week 12 or week 52, respectively. Data were analyzed using SAS version 8.2 (SAS Institute, Cary, North Carolina, USA).

Results

Patient disposition and baseline characteristics

Patient disposition and baseline characteristics for the overall study population have been described previously [19]. Briefly, 1275 patients entered the single-blind placebo run-in period, of whom 1124 were randomized to double-blind treatment with aliskiren 150 mg ($n = 459$), HCTZ 12.5 mg ($n = 444$) or placebo ($n = 221$). A total of 918 patients (81.7% of the randomized patient population) completed 52 weeks of treatment.

In the subgroup of patients who were obese ($n = 396$), baseline and demographic characteristics were well matched across the aliskiren and HCTZ groups (Table 1). Compared with nonobese patients ($n = 721$), the obese subgroup had a higher incidence of diabetes (17.4 vs. 7.4%) and metabolic syndrome (66.7 vs. 29.5%). Patients in the obese subgroup had a mean BMI of 34.0 kg/m^2, compared with 26.3 kg/m^2 in the nonobese subgroup. Mean baseline BP was similar in the two groups (154.5/99.2 vs. 154.2/98.8 mmHg in the obese and nonobese subgroups, respectively).

Blood pressure reductions in obese and nonobese patients

In obese patients, least-squares mean BP reductions at week 12 endpoint were significantly greater with aliskiren monotherapy than with HCTZ monotherapy (16.7/12.3 vs. 12.2/9.1 mmHg, $P = 0.001$ for msSBP and $P < 0.0001$ for msDBP; Fig. 2). At week 52 endpoint, aliskiren-based treatment resulted in BP reductions of 19.9/15.5 mmHg, compared with 17.6/13.3 mmHg with HCTZ-based treatment; the reduction in msDBP observed with aliskiren was significantly larger than that with HCTZ ($P < 0.01$). Overall, 87/183 obese patients (47.5%) in the aliskiren group had received add-on amlodipine at week 52 endpoint, compared with 78/150 (52.0%) in the HCTZ group.

BP response rates were significantly greater with the aliskiren regimen than with the HCTZ regimen in the obese subgroup at both week 12 endpoint (71.2 vs. 59.5%, $P < 0.05$) and week 52 endpoint (86.3 vs. 78.0%, $P < 0.05$) (Fig. 2c). Significantly more obese patients achieved BP control with aliskiren monotherapy than with HCTZ monotherapy at week 12 endpoint (60.6 vs. 44.3%,

Table 1 Patient baseline and demographic characteristics (safety population)

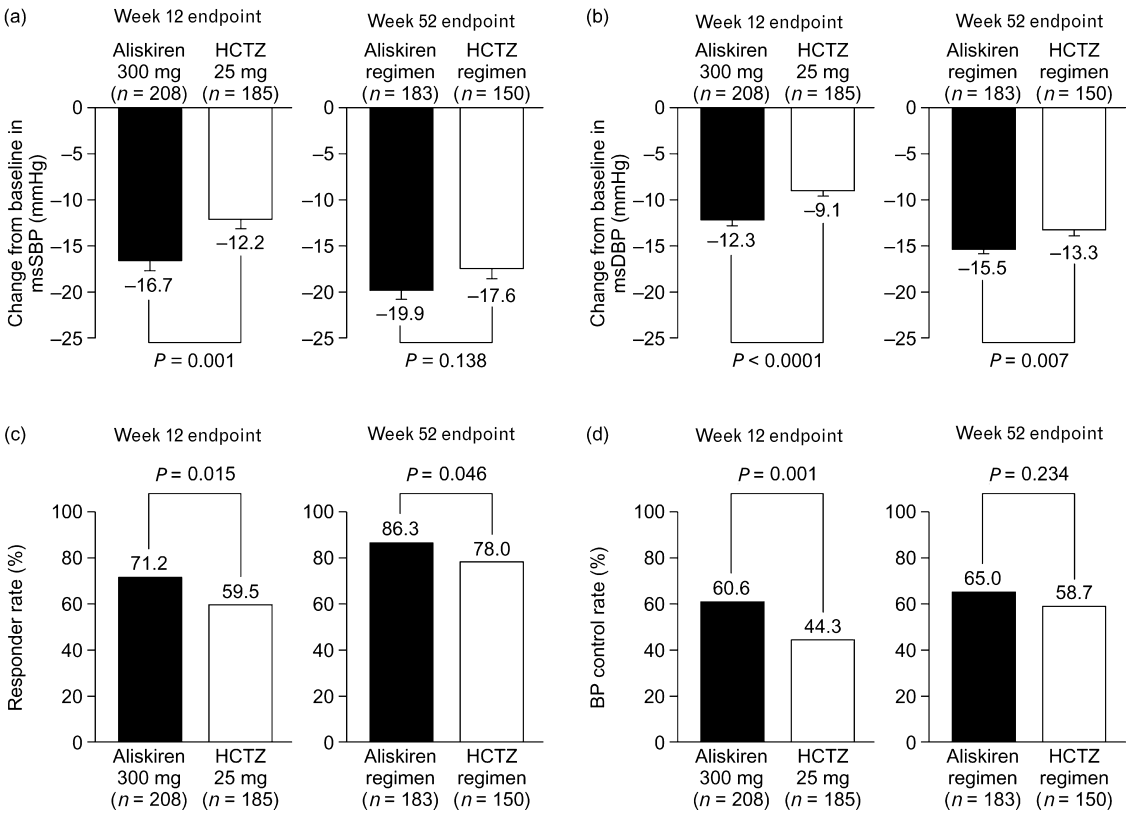
Parameter	Obese patients[a]			Total nonobese patients ($n=721$)
	Aliskiren ($n=208$)	HCTZ ($n=188$)	Total ($n=396$)	
Age (years)	54.9 ± 10.6	54.0 ± 10.6	54.5 ± 10.6	56.7 ± 10.9
Male (%)	55.3%	49.5%	52.5%	56.4%
Race (*n*) (%) Caucasian Asian Other	207 (99.5%) 1 (0.5%) 0 (0)	187 (99.5%) 1 (0.5%) 0 (0)	394 (99.5%) 2 (0.5%) 0 (0)	713 (98.9%) 7 (1.0%) 1 (0.1%)
BMI (kg/m^2)	33.6 ± 3.4	34.4 ± 4.1	34.0 ± 3.7	26.3 ± 2.4
Diabetes (*n*) (%)	39 (18.8%)	30 (16.0%)	69 (17.4%)	53 (7.4%)
Metabolic syndrome (*n*) (%)[b]	139 (66.8%)	125 (66.5%)	264 (66.7%)	213 (29.5%)
msSBP (mmHg)	155.0 ± 10.7	154.0 ± 11.8	154.5 ± 11.2	154.2 ± 10.9
msDBP (mmHg)	99.4 ± 3.6	99.0 ± 3.6	99.2 ± 3.6	98.8 ± 3.2

Values are presented as mean ± SD unless otherwise stated. [a] Obesity was defined as BMI ≥ 30 kg/m^2. [b] Metabolic syndrome was defined as any three of the following, according to National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria [35]: waist circumference more than 102 cm for men or more than 88 cm for women; triglycerides at least 150 mg/dl (≥1.69 mmol/l); high-density lipoprotein cholesterol less than 40 mg/dl (<1.04 mmol/l) for men or less than 50 mg/dl (<1.29 mmol/l) for women; blood pressure at least 130/85 mmHg; fasting glucose at least 110 mg/dl (≥6.1 mmol/l).BMI, body mass index; HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

$P=0.0013$). BP control rates were similar in the two treatment groups at week 52 endpoint (Fig. 2d).

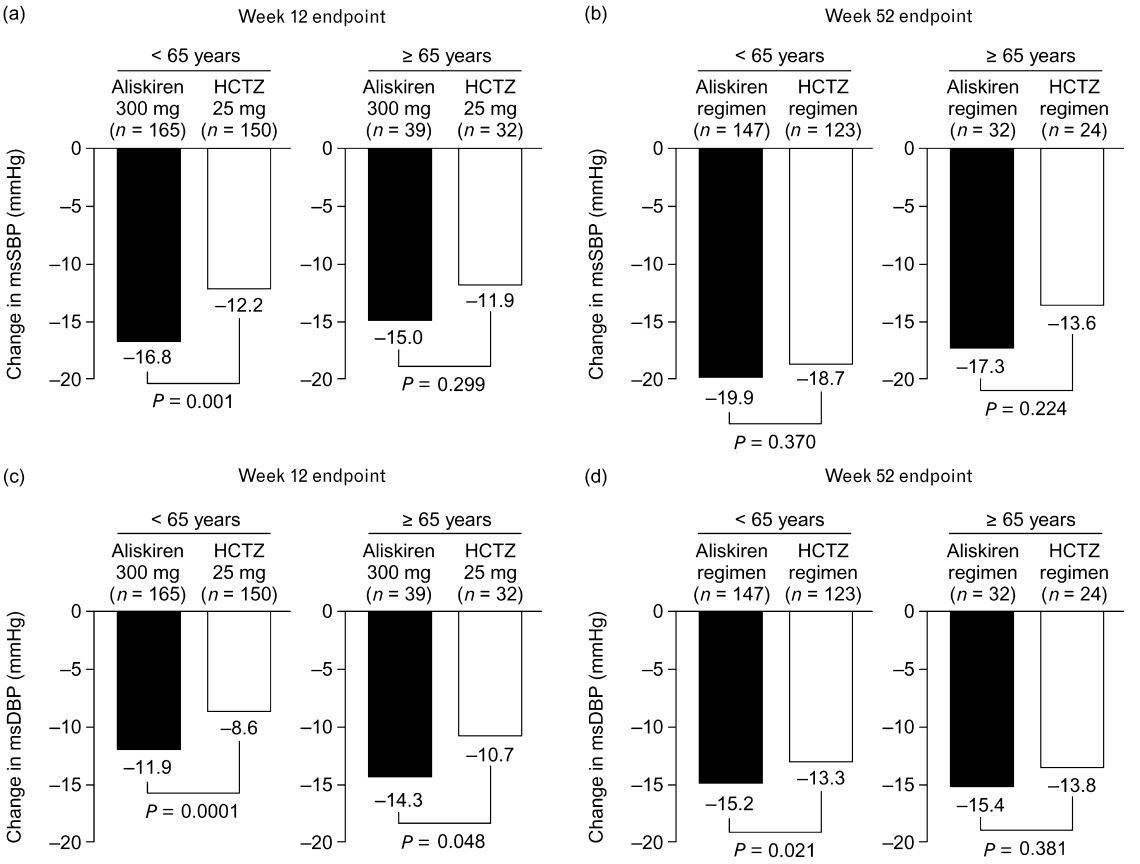
BP reductions from baseline following treatment with aliskiren monotherapy were similar in the obese and nonobese patients at week 12 endpoint (−16.7/−12.3 vs. −17.1/−12.3, $P=$NS) and were also similar with the aliskiren-based regimen between subgroups at week 52 endpoint (−19.9/−15.5 vs. −21.1/−15.6 mmHg, $P=$NS). By contrast, reductions in BP from baseline

Fig. 2



Changes in (a) mean sitting systolic blood pressure (b) mean sitting diastolic blood pressure, (c) proportion of patients responding to treatment and (d) achieving blood pressure control in the obese patient subgroup at week 12 and week 52 endpoints. At week 12 endpoint all patients were receiving monotherapy. From week 12, patients not achieving BP less than 140/90 mmHg could receive add-on amlodipine 5 mg, titrated to 10 mg from week 18. Changes from baseline are least-squares mean ± SEM. Response to treatment was defined as msDBP less than 90 mmHg and/or at least 10 mmHg reduction from baseline. BP control was defined as BP less than 140/90 mmHg. Data are shown for the obese subgroup of the intent-to-treat population. BP, blood pressure; HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

Fig. 3



Changes in mean sitting systolic blood pressure at (a) week 12 endpoint and (b) week 52 endpoint, and mean sitting diastolic blood pressure at (c) week 12 endpoint and (d) week 52 endpoint in obese patients aged less than 65 and at least 65 years. At week 12 endpoint all patients were receiving monotherapy. From week 12, patients not achieving BP less than 140/90 mmHg could receive add-on amlodipine 5 mg, titrated to 10 mg from week 18. Changes from baseline are least-squares mean ± SEM. Data are shown for the obese subgroup of the intent-to-treat population. BP, blood pressure; HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

with the HCTZ-based regimen were significantly smaller in obese patients vs. nonobese patients at both week 12 endpoint (−12.2/−9.1 vs. −15.7/−11.3 mmHg, $P = 0.005$ for msSBP and $P = 0.002$ for msDBP) and week 52 endpoint (−17.6/−13.3 vs. −20.8/−15.4 mmHg, $P = 0.012$ for msSBP and $P = 0.006$ for msDBP). In the overall study population, aliskiren 300 mg monotherapy reduced BP from baseline by 17.4/12.2 mmHg at week 12 endpoint (compared with 14.7/10.3 mmHg with HCTZ 25 mg monotherapy, $P < 0.001$), and aliskiren-based therapy provided BP reductions of 22.1/16.0 mmHg from baseline at week 52 endpoint (compared with 21.2/15.0 mmHg with HCTZ-based therapy, $P < 0.05$ for DBP, $P =$ NS for SBP) [19].

A *post hoc* analysis of the subgroups of obese patients aged less than 65 years and at least 65 years was performed to investigate the influence of age on BP reductions with an aliskiren-based or HCTZ-based regimen (Fig. 3). Compared with HCTZ-based treatment, aliskiren-based treatment in patients aged less than 65 years provided significantly greater msDBP reductions at week 12 endpoint ($P = 0.0001$) and week 52 endpoint ($P = 0.0211$), and significantly greater msSBP reductions at week 12 endpoint ($P = 0.0011$). In patients aged at least 65 years, msDBP and msSBP reductions were numerically greater with the aliskiren regimen than the HCTZ regimen at week 12 endpoint and week 52 endpoint.

Safety and tolerability

Study treatments were generally well tolerated. Rates of adverse events were slightly higher in obese patients than in nonobese patients (70.2 vs. 62.3%; Table 2). Adverse events were mostly mild or moderate in intensity, and few patients discontinued the study because of adverse events (7.1% of obese patients and 5.8% of nonobese patients).

Headache was the most frequently reported adverse event in the obese subgroup, and was reported significantly more often with HCTZ treatment than with aliskiren treatment [25 patients (13.3%) vs. 13 patients (6.3%); $P = 0.017$]. Peripheral edema, nasopharyngitis,

Table 2 Safety and tolerability of study treatments by subgroup (safety population)

	Obese patients[a]				
Category	Aliskiren ($n=208$)	HCTZ ($n=188$)	Total ($n=396$)	*P* value	Total nonobese patients ($n=721$)
Any AE	150 (72.1%)	128 (68.1%)	278 (70.2%)	0.381	449 (62.3%)
Discontinuations due to AEs	12 (5.8%)	16 (8.5%)	28 (7.1%)	0.288	42 (5.8%)
Most frequently reported individual AEs					
Headache	13 (6.3%)	25 (13.3%)	38 (9.6%)	0.017	63 (8.7%)
Peripheral edema	18 (8.7%)	13 (6.9%)	31 (7.8%)	0.520	31 (4.3%)
Nasopharyngitis	13 (6.3%)	13 (6.9%)	26 (6.6%)	0.790	29 (4.0%)
Back pain	9 (4.3%)	13 (6.9%)	22 (5.6%)	0.262	31 (4.3%)
Dizziness	6 (2.9%)	11 (5.9%)	17 (4.3%)	0.146	33 (4.6%)
Hypertriglyceridemia	11 (5.3%)	6 (3.2%)	17 (4.3%)	0.304	11 (1.5%)
Hypercholesterolemia	10 (4.8%)	7 (3.7%)	17 (4.3%)	0.595	28 (3.9%)
Diarrhea	7 (3.4%)	5 (2.7%)	12 (3.0%)	0.682	21 (2.9%)
Arthralgia	7 (3.4%)	7 (3.7%)	14 (3.5%)	0.847	21 (2.9%)
Bronchitis	6 (2.9%)	4 (2.1%)	10 (2.5%)	0.754	23 (3.2%)
Cough	7 (3.4%)	8 (4.3%)	15 (3.8%)	0.643	23 (3.2%)
Eczema	12 (5.8%)	4 (2.1%)	16 (4.0%)	0.077	15 (2.1%)
Fatigue	2 (1.0%)	7 (3.7%)	9 (2.3%)	0.092	25 (3.5%)
Abnormal laboratory values					
Serum potassium	$n=205$	$n=179$	$n=384$		$n=698$
<3.5 mmol/l	2 (1.0%)	25 (14.0%)	27 (7.0%)	<0.0001	74 (10.6%)
>5.5 mmol/l	14 (6.8%)	10 (5.6%)	24 (6.3%)	0.6158	32 (4.6%)
≥ 6.0 mmol/l	8 (3.9%)	4 (2.2%)	12 (3.1%)	0.3936	13 (1.9%)
BUN	$n=205$	$n=179$	$n=384$		$n=699$
>14.28 mmol/l	1 (0.5%)	1 (0.6%)	2 (0.5%)	>0.999	5 (0.7%)
Creatinine	$n=205$	$n=179$	$n=384$		$n=699$
>176.8 μmol/l	0	0	0	NA	2 (0.3%)

Values are presented as the number (%) of patients. [a]Obesity was defined as body mass index ≥ 30 kg/m^2.AE, adverse event; BUN, blood urea nitrogen; HCTZ, hydrochlorothiazide; NA, not applicable.

hypertriglyceridemia and eczema were all reported more frequently in obese patients than in nonobese patients, but there was no noticeable difference in incidence between treatment groups.

In the overall safety population, serious adverse events (SAEs) were reported by 26 (4.6%) patients receiving the aliskiren regimen and 22 (3.9%) patients receiving the HCTZ regimen. Three SAEs were suspected by the investigator to be related to the study drug: one patient receiving aliskiren 150 mg experienced a burning stomach pain; one patient receiving placebo had a myocardial infarction; one patient receiving HCTZ 25 mg had moderate hypokalemia. All three patients were discontinued from the study.

In obese patients, hypokalemia (serum potassium levels <3.5 mmol/l) occurred more frequently with the HCTZ-based regimen than with the aliskiren-based regimen (14.0 vs. 1.0%, $P<0.0001$). Elevated serum potassium levels (>5.5 mmol/l) occurred slightly more frequently with the aliskiren-based regimen than with the HCTZ-based regimen in obese patients (6.8 vs. 5.6%, $P=$NS).

Discussion

Obesity and hypertension are frequently linked, and the pathophysiology of hypertension in obese patients differs from that in lean patients [2–6]. Despite this, treatment guidelines do not provide specific recommendations for antihypertensive drug therapy in obese patients [7,8]. Few clinical trials have been performed in obese patients, so the evidence base for their treatment options is small [12]. We recently reported the results of a large, randomized clinical trial in 1124 patients with hypertension in which a treatment regimen based on the direct renin inhibitor aliskiren was shown to provide significantly greater BP reductions over 52 weeks than an HCTZ-based regimen [19]. Here, we report the results of a *post hoc* analysis of the subgroup of obese patients in our trial. In obese patients, aliskiren monotherapy provided significantly greater BP reductions than HCTZ monotherapy after 12 weeks' treatment, and the aliskiren-based regimen lowered BP more effectively than the HCTZ-based regimen (both with optional addition of amlodipine) over 52 weeks. Aliskiren-based treatment was generally well tolerated in obese and nonobese patients, and was associated with a clearly lower incidence of hypokalemia and slightly higher rate of hyperkalemia than HCTZ-based treatment in both patient subgroups.

In obese patients, aliskiren 300 mg monotherapy reduced BP by 16.7/12.3 mmHg at week 12 endpoint, representing a significant additional BP reduction of 4.5/3.2 mmHg over HCTZ 25 mg monotherapy. Almost two-thirds (60.6%) of obese patients achieved BP control (BP $<140/90$ mmHg) with aliskiren 300 mg monotherapy,

compared with fewer than half of patients (44.3%) receiving HCTZ 25 mg monotherapy. Significantly larger msDBP reductions and responder rates were also observed with the aliskiren-based regimen compared with the HCTZ-based regimen at week 52 endpoint, despite the addition of amlodipine to achieve BP control in both treatment groups. Indeed, fewer patients in the aliskiren group required add-on amlodipine compared with the HCTZ group. These findings reflect the fact that HCTZ, either as monotherapy or with optional addition of amlodipine, was significantly less effective for lowering BP in obese patients than in nonobese patients, whereas mean reductions in BP from baseline with aliskiren monotherapy or the aliskiren-based regimen were similar in the obese and nonobese patient subgroups. The larger BP reductions from baseline with aliskiren compared with HCTZ in obese patients may reflect the beneficial effects of renin system inhibition in adipose tissue, as increased angiotensin II generation in adipocytes contributes to elevated BP in obese patients with hypertension [20]. Conversely, it may be that the obese patients ingested more food and/or dietary salt compared with nonobese patients, and this could have reduced the antihypertensive efficacy of the thiazide diuretic. Importantly, increased salt intake would suppress renin system activity and thus would be expected to reduce the BP-lowering effect of aliskiren in obese patients compared with nonobese patients, yet mean BP reductions from baseline in the present study were similar in obese and nonobese patients.

The finding that aliskiren provides greater BP reductions from baseline compared with HCTZ in obese patients is noteworthy, given that the United States guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7 guidelines) recommend the use of thiazide diuretics as first-line therapy for the treatment of hypertension [7], and neither the United States nor European hypertension guidelines make specific recommendations for the treatment of hypertension in obese patients [7,8]. Previous studies have shown that obesity can affect the efficacy of antihypertensive agents [12,21]; in a trial in 42 lean and obese patients with hypertension, the β-blocker metoprolol lowered BP more effectively than the calcium channel blocker isradipine in obese patients, whereas isradipine was more effective in lean patients [12]. These results suggest that inhibition of the renin–angiotensin system may be the optimal way to treat hypertension in obese patients. Indeed, aliskiren, which reduces plasma renin activity more than β-blockers [22] and more completely than angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) [23,24], may be the best way to inhibit this system.

Although cross-study comparisons should be made with caution, it is interesting to set the BP control rates achieved with aliskiren-based and HCTZ-based therapies in obese patients in this study in the context of the effects of other antihypertensive agents in previous studies in this patient group. The rate of BP control to less than 140/90 mmHg achieved with aliskiren 300 mg monotherapy at week 12 endpoint in our *post hoc* analysis (60.6%) was similar to that seen previously after 12 weeks' treatment with lisinopril 40 mg (60%) [25], even though baseline BP was markedly higher in obese patients in our study (159.3/95.0–160.8/96.1 mmHg) than in the lisinopril trial (142.1/88.3–146.3/90.0 mmHg). BP control rates with aliskiren-based therapy were higher than the rates of 34 and 38% achieved with 13 weeks of valsartan-based or atenolol-based treatment, respectively, in a study of 132 obese patients with mild-to-moderate hypertension [21]. These results suggest that aliskiren may represent a valid first-line option for the treatment of hypertension in obese patients.

Different antihypertensive agents may provide different BP-lowering effects in older and younger patients; indeed, treatment guidelines from the British Hypertension Society recommend using diuretics or calcium channel blockers in patients older than 55, rather than ACE inhibitors, ARBs or β-blockers [26]. In the present study, between-treatment differences in BP reductions in obese patients aged less than 65 years were consistent with the analyses in the overall obese patient population. In older patients (aged $\geq$ 65 years), aliskiren-based treatment provided numerically (but not significantly) greater reductions than HCTZ-based treatment at week 12 endpoint and week 52 endpoint. Importantly, there were few obese patients aged at least 65 years (fewer than 40 in each treatment group) and so the observation that between-treatment differences were not statistically significant may simply reflect the small patient numbers in this subgroup. Indeed, the differences in least-squares mean BP reductions between the aliskiren and HCTZ regimens in the at least 65 years subgroup were numerically similar to those observed in the less than 65 years subgroup. A previous subgroup analysis in the overall ITT population showed that the aliskiren regimen provided significantly greater reductions in msSBP and pulse pressure than the HCTZ regimen in patients aged at least 65 years and at least 75 years at week 52 endpoint [27].

Aliskiren-based treatment was well tolerated over 52 weeks in obese and nonobese patients. The overall incidence of adverse events was similar with the aliskiren and HCTZ-based regimens, although significantly more obese patients receiving the HCTZ-based regimen reported headache. Peripheral edema, nasopharyngitis, hypertriglyceridemia and eczema occurred more frequently in obese patients than in nonobese patients, but there were no notable between-treatment differences in the incidence of these adverse events. Importantly, the incidence of hypokalemia (serum potassium

levels <3.5 mmol/l) was significantly lower with the aliskiren-based regimen than with the HCTZ-based regimen. Hypokalemia is a well known side effect of thiazide diuretics, and is associated with impaired glucose tolerance, increased risk of new-onset diabetes, and sudden cardiac death [28–31]. As obesity is itself a risk factor for type 2 diabetes [32], this effect of thiazide diuretics may be of concern in obese patients. The incidence of hyperkalemia was slightly higher with aliskiren-based treatment that with HCTZ-based treatment in obese and nonobese patients, as would be expected when comparing a thiazide diuretic with an antihypertensive agent that targets the renin system.

As with any *post hoc* analysis, the data presented here must be interpreted with caution. Nonetheless, baseline and demographic characteristics were generally well matched between the aliskiren and HCTZ treatment arms, and baseline BP was similar in the obese and nonobese patient subgroups; between-group and within-group comparisons are therefore valid. Further studies conducted specifically in obese patients are required to support the results of this study. Compared with nonobese patients, obese patients showed a higher incidence of diabetes (17.4 vs. 7.4%) and metabolic syndrome (66.7 vs. 29.5%), consistent with the known relationship between obesity and metabolic disorders such as diabetes [33,34].

The limitations of the present study should be noted. After week 12, amlodipine 5–10 mg was added in patients not achieving BP control. The effects of adding a calcium channel blocker to inhibitors of the renin system are additive, whereas addition to a thiazide diuretic is less than additive. Thus, comparison of BP reductions after week 12 may be less informative than BP reductions at week 12 endpoint. However, it is important to note that fewer aliskiren-treated patients than HCTZ-treated patients required addition of amlodipine to achieve BP control, implying greater efficacy of aliskiren compared with HCTZ over 52 weeks in obese patients. A further limitation was the choice of HCTZ dose. HCTZ 25 mg is not the maximum approved dose, and BP reductions with maximum-dose HCTZ and maximum-dose aliskiren might be expected to be of a similar magnitude. However, HCTZ 25 mg is the maximum dose commonly used in clinical practice for antihypertensive treatment. Finally, it would have been interesting to assess the effects of aliskiren treatment on 24-h ambulatory BP. Further studies measuring changes in BP over 24 h in obese patients are warranted.

In conclusion, this *post hoc* analysis showed that, in obese patients with hypertension, aliskiren monotherapy and aliskiren-based therapy (with optional addition of amlodipine) provided greater BP reductions than HCTZ monotherapy and HCTZ-based therapy (also with optional addition of amlodipine), respectively. These findings reflect the fact that aliskiren-based treatment provided similar BP lowering compared with baseline in obese and nonobese patients, whereas in patients who received HCTZ-based treatment, BP reductions compared with baseline were significantly smaller in obese patients compared with patients who were not obese. Aliskiren-based treatment was well tolerated, and was associated with a significantly lower incidence of hypokalemia than the HCTZ-based regimen. Direct renin inhibition with aliskiren may therefore represent a superior alternative to HCTZ as a first-line treatment option for the management of hypertension in obese patients.

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