Direct Renin Inhibition With Aliskiren in Obese Patients With Arterial Hypertension

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Abstract—Current guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend first-line treatment with a thiazide diuretic but do not provide specific guidance for obese patients. The renin system is activated in obesity-associated arterial hypertension. Therefore, we tested the hypothesis that the oral direct renin inhibitor aliskiren could provide additive blood pressure lowering in obese patients with hypertension (body mass index $\geq$30 kg/m^2; mean sitting diastolic blood pressure: 95 to 109 mm Hg) who had not responded to 4 weeks of treatment with hydrochlorothiazide (HCTZ) 25 mg. After a 2- to 4-week washout, 560 patients received single-blind HCTZ (25 mg) for 4 weeks; 489 nonresponders were randomly assigned to double-blind aliskiren (150 mg), irbesartan (150 mg), amlodipine (5 mg), or placebo for 4 weeks added to HCTZ (25 mg), followed by 8 weeks on double the initial doses of aliskiren, irbesartan, or amlodipine. After 8 weeks of double-blind treatment (4 weeks on the higher dose), aliskiren/HCTZ lowered blood pressure by 15.8/11.9 mm Hg, significantly more ($P<0.0001$) than placebo/HCTZ (8.6/7.9 mm Hg). Aliskiren/HCTZ provided blood pressure reductions similar to those with irbesartan/HCTZ and amlodipine/HCTZ (15.4/11.3 and 13.6/10.3 mm Hg, respectively), with similar tolerability to placebo/HCTZ. Adverse event rates were highest with amlodipine/HCTZ because of a higher incidence of peripheral edema (11.1% versus 0.8% to 1.6% in other groups). In conclusion, combination treatment with aliskiren is a highly effective and well-tolerated therapeutic option for obese patients with hypertension who fail to achieve blood pressure control with first-line thiazide diuretic treatment. (***Hypertension*. 2007;49:1047-1055.**)

Key Words: direct renin inhibitor ■ Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 ■ obesity ■ renin–angiotensin system ■ thiazide diuretic

The proportion of hypertensive patients who are obese has increased steadily in recent years. Given that 75% of obese patients have hypertension, but <20% have their blood pressure (BP) controlled to <140/90 mm Hg,[1] there is a clear need for new antihypertensive treatment options for this patient group. Yet, current guidelines do not provide specific guidance for the treatment of this patient population,[2] and data from larger clinical trials addressing the issue are lacking. This state of affairs is surprising, because the underlying pathophysiology differs between lean and obese patients with arterial hypertension. In particular, obesity-associated hypertension involves activation of the renin system,[3,4] volume expansion, and increased cardiac output[5–7] rather than systemic vasoconstriction. Combination of a low dose of a thiazide diuretic with a renin system inhibitor may, therefore, be a suitable treatment approach.[8] Aliskiren is the first in a new class of direct renin inhibitors.[9,10] Combination treatment with a renin system inhibitor is a theoretically attractive approach for patients with an insufficient response to first-line diuretic treatment. Renin system inhibition blocks the effects of the counterregulatory rise in renin release from the kidney that occurs in response to sodium depletion and thereby enhances the BP-lowering effects of diuretic treatment.[11] Combination of aliskiren with hydrochlorothiazide (HCTZ) in patients with hypertension has been shown to provide significant further reductions in BP with no negative effects on safety and tolerability.[12] Moreover, the incidence of hypokalemia (a common adverse effect of thiazide diuretic treatment) with HCTZ is reduced by combination with aliskiren.[12] This effect is also observed with other renin system inhibitors and may reduce the risk of thiazide-induced glucose intolerance, because low potassium levels on diuretic treatment are associated with increased plasma glucose concentrations.[13] Other clinical studies have shown that aliskiren exhibits BP-lowering efficacy comparable to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers,[14–16] with placebo-like tolerability.[16,17] The aim of this study was to investigate the antihypertensive efficacy and safety of aliskiren as combination therapy for obese patients with arterial hypertension who did not achieve adequate BP

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control with HCTZ treatment. The BP-lowering effects and tolerability of combination with aliskiren over 12 weeks of double-blind treatment were compared with continued treatment with HCTZ alone and with combination treatment with the angiotensin receptor blocker irbesartan or the calcium channel blocker amlodipine.

Methods

Patients

Eligible patients were men and women aged ≥18 years with hypertension (mean sitting diastolic BP [msDBP] ≥95 and <110 mm Hg at baseline) and body mass index (BMI) ≥30 kg/m^2. Patients with msDBP ≥110 mm Hg or mean sitting systolic BP (msSBP) ≥180 mm Hg were excluded, as were patients with secondary hypertension, type 1 or 2 diabetes mellitus, history of severe cardiovascular or cerebrovascular disease, or other severe or life-threatening disease. Patients with any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of the study drugs were also excluded.

All of the patients provided written informed consent, and the study protocol was approved by local ethical committee and/or appropriate institutional review boards. The study was conducted in accordance with Good Clinical Practice guidelines and in compliance with the Declaration of Helsinki (2002) and Title 45 of the United States Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Study Design

This was a randomized, double-blind, multicenter trial conducted in 69 centers in Belgium, France, Germany, Israel, Norway, Russia, and Spain. The first patient was enrolled on June 3, 2005, and the last patient completed on April 27, 2006.

The study design is shown in Figure 1. After screening and a 2- to 4-week washout for patients receiving antihypertensive medication, eligible patients (msDBP ≥95 and <110 mm Hg) received single-blind HCTZ (25 mg) once daily for 4 weeks. Patients with a successful response to HCTZ (msDBP <90 mm Hg) were discontinued from the study. Nonresponders (msDBP ≥90 and <110 mm Hg) who fulfilled study inclusion criteria were randomly assigned to double-blind, once-daily aliskiren (150 mg), irbesartan (150 mg), amlodipine (5 mg), or placebo in addition to continuing HCTZ (25 mg) once daily. Random assignment was performed using the interactive voice response system provider. After 4 weeks, the doses of aliskiren, irbesartan, and amlodipine were doubled, and treatment continued for a further 8 weeks.

Patients with msDBP ≥110 mm Hg or msSBP ≥180 mm Hg at any time were permanently discontinued from the study. Patients were also discontinued for safety reasons if they exhibited msDBP ≥100 mm Hg or msSBP ≥160 mm Hg at or any time after week 8 of the double-blind treatment period. Because of this withdrawal criterion, the week 8 end point was used for intent-to-treat analysis of the primary efficacy variable.

All of the study medications were taken with water at ≈8:00 AM, except on the morning of clinic visits. A double-dummy technique was used to maintain double-blind conditions; all of the patients took 3 capsules and 2 tablets of study medication per day. Throughout the study, patients were not permitted to take additional drugs indicated for the treatment of hypertension or any other medication that could interfere with the evaluation of safety, tolerability, and/or efficacy of study drugs.

Study Objectives

The primary objective of this study was to compare the change from baseline to the week 8 end point in msDBP with aliskiren (300 mg)/HCTZ (25 mg) with that of HCTZ (25 mg) alone in obese patients with hypertension who did not achieve BP control with 25 mg of HCTZ. Secondary objectives included comparisons of msSBP and msDBP reductions with the aliskiren/HCTZ group with those obtained with the irbesartan/HCTZ, amlodipine/HCTZ, and placebo/HCTZ groups at weeks 4, 8, and 12 the proportion of patients with a successful response to treatment (msDBP: <90 mm Hg or a ≥10 mm Hg reduction from baseline) or achieving BP control (mean sitting BP: <140/90 mm Hg) and safety and tolerability.

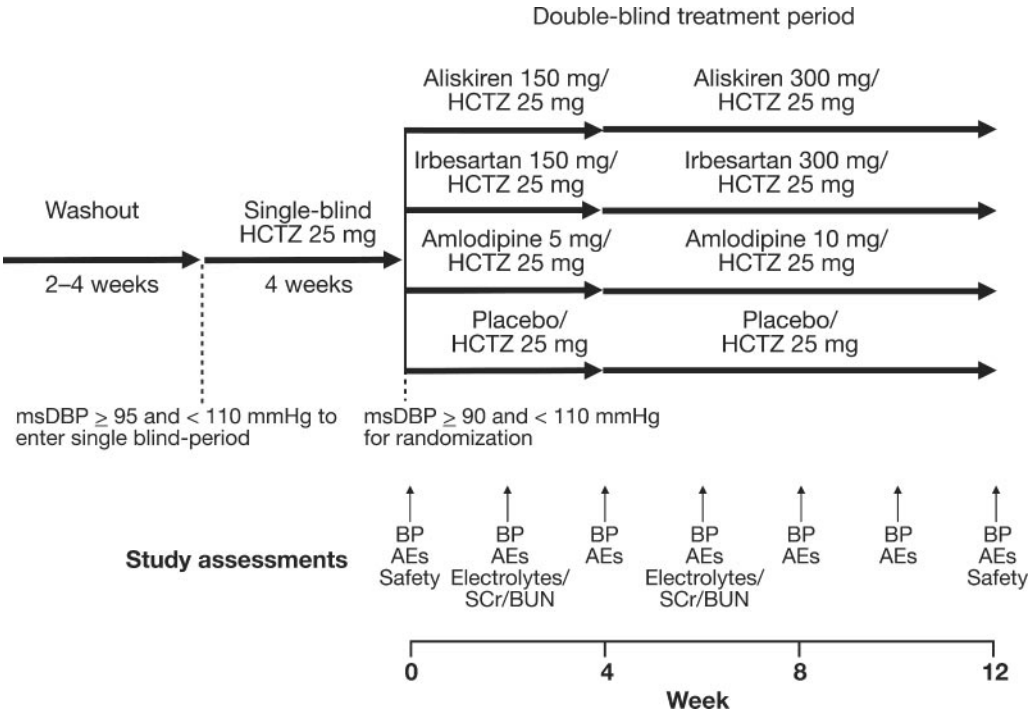

Figure 1. Study design. Vertical arrows denote clinic visits and assessments. AEs indicate assessment of adverse events; BUN, blood urea nitrogen; Safety, safety assessments (complete physical examination, laboratory evaluations, and ECG); SCr, serum creatinine.

BP Measurements

Clinic BP was measured using a mercury sphygmomanometer and appropriate cuff size (in accordance with the 2005 American Heart Association Committee on Blood Pressure Determination).[18] Sitting BP was measured at trough (24±3 hours after dose) at each clinic visit in the arm that recorded the highest BP measurement at the first visit. After sitting for 5 minutes, 3 sitting BP measurements were made at 1- to 2-minute intervals, and the mean value was taken as the average BP for that visit.

Biomarker Assessments

Plasma renin activity (PRA) was measured by radioimmunoassay (DiaSorin) in a subset of patients at pretreatment (postwashout) baseline and at the start and end of double-blind treatment.

Safety and Tolerability Assessments

Safety assessments consisted of the recording of all adverse events, measurement of vital signs, routine laboratory investigations (hematology, urinalysis, and blood chemistry), physical examination, and ECG (Figure 1). The safety population was composed of all of the patients who received ≥1 dose of double-blind study medication.

Statistical Analyses

A sample size of 444 patients completing double-blind treatment (randomized population of 496 patients assuming a 10% dropout rate) was targeted with equal randomization among treatment groups. This sample size provided 90% power to detect a 3.5-mm Hg treatment difference in the primary efficacy variable between aliskiren/HCTZ and HCTZ alone (assuming SD for msDBP of 8 mm Hg).

To randomly assign 496 patients into the double-blind treatment period, it was estimated that as many as 1420 patients would need to be enrolled into the single-blind phase. However, there were fewer responders to single-blind treatment than anticipated, and the planned double-blind sample size was achieved after enrollment of 560 patients.

Changes from baseline in msDBP and msSBP at week 4 end point, week 8 end point, and week 12 were analyzed for the intent-to-treat (ITT) population (all randomly assigned patients with a baseline measurement and ≥1 postbaseline efficacy measurement during the double-blind period) using a 2-way ANCOVA model with treatment and region as factors and centered baseline as covariate. Responder and BP control rates were analyzed for the ITT population using a logistic regression model with treatment and region as factors and centered baseline measure as covariate. The week 4 and 8 end points were defined as the last postbaseline measurement before week 4 or 8, respectively, if the actual measurement for that week was missing.

Changes in PRA (which is not normally distributed) from pretreatment baseline (week −4) with each double-blind treatment at week 12 were calculated as the geometric mean ratio of change from baseline for patients in each double-blind randomly assigned group. For calculation of the change in PRA with single-blind HCTZ (at week 0 versus pretreatment baseline at week −4), data from all of the patients were pooled for clarity.

All of the statistical tests were performed at a 2-sided significance level of 0.05, and 95% CIs were provided for differences between treatment groups. Data were analyzed by Novartis using SAS 8.2 (SAS Institute).

Results

Patient Disposition and Baseline Characteristics

A total of 560 patients entered the single-blind phase, of whom 489 were randomly assigned to double-blind aliskiren/HCTZ (n=122), irbesartan/HCTZ (n=119), amlodipine/HCTZ (n=126), or placebo/HCTZ (n=122; Figure 2). The ITT population was the same as the randomly assigned population for all of the groups except placebo/HCTZ (n=120). Nearly half (35 of 71) of the patients who discontinued single-blind treatment did so because of abnormal test procedure results; this definition included those patients showing successful BP control with HCTZ (msDBP <90 mm Hg) who were automatically discontinued according to the study protocol.

Overall, 41 patients discontinued double-blind treatment before the end of the study (Figure 2); major reasons were adverse events (17 patients, 41.5% of discontinuations), withdrawal of consent (8 patients, 19.5%), and unsatisfactory therapeutic effect (8 patients, 19.5%). Withdrawal of consent was mainly because of personal reasons; the majority of discontinuations because of unsatisfactory therapeutic effect (5 of 8 discontinuations) that occurred with placebo/HCTZ.

Baseline characteristics showed that the treatment groups were well matched (Table 1). Randomly assigned patients had an average age of 54.1 years and a BMI of 34.4 kg/m^2; almost all of the patients were white. More than two thirds of patients (67.7%) fulfilled the National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria for metabolic syndrome.[19]

Changes in msDBP and msSBP

Aliskiren (300 mg) added to HCTZ (25 mg) caused significant reductions in msDBP and msSBP compared with HCTZ (25 mg) alone (placebo/HCTZ) at week 8 end point (mean treatment difference: −4.0 and −7.2 mm Hg, respectively; $P<0.0001$; Figure 3a and 3b and Table 2). The reductions in msDBP and msSBP achieved with aliskiren/HCTZ were also significantly greater than those observed with HCTZ alone at the week 4 end point ($P=0.016$ for msDBP and $P=0.005$ for msSBP) and week 12 ($P=0.005$ and $P<0.0001$; Figure 3c and 3d).

Aliskiren (300 mg)/HCTZ (25 mg) caused numerically larger reductions in msDBP and msSBP compared with irbesartan (300 mg)/HCTZ (25 mg) and amlodipine (10 mg)/HCTZ (25 mg) at week 8 end point, but there were no statistically significant differences between treatment groups (Figure 3a and 3b and Table 2). As expected, doubling the dose of aliskiren from 150 to 300 mg led to greater BP reductions (least-squares mean change in msSBP/DBP: −15.8/−11.9 mm Hg at week 8 end point versus −9.4/−7.8 mm Hg at week 4 end point; Figure 3c and 3d). Further BP reductions were also observed after titration of irbesartan and amlodipine.

Responder and BP Control Rates

Responder rates were significantly higher with aliskiren/HCTZ than HCTZ alone at week 8 end point ($P=0.0193$; Figure 4a) and at week 12 (76.1% versus 57.7%; $P=0.004$). The percentage of patients achieving BP control (<140/90 mm Hg) was also significantly higher with aliskiren/HCTZ than HCTZ alone at week 8 end point ($P=0.0005$; Figure 4b) and at week 12 (58.4% versus 33.3%; $P=0.0001$).

Responder rates and BP control rates with amlodipine/HCTZ and irbesartan/HCTZ were not significantly different from those observed with aliskiren/HCTZ at week 8 end point (Figure 4) or week 12. The BP control rate with aliskiren/HCTZ at week 8 end point was numerically higher than that

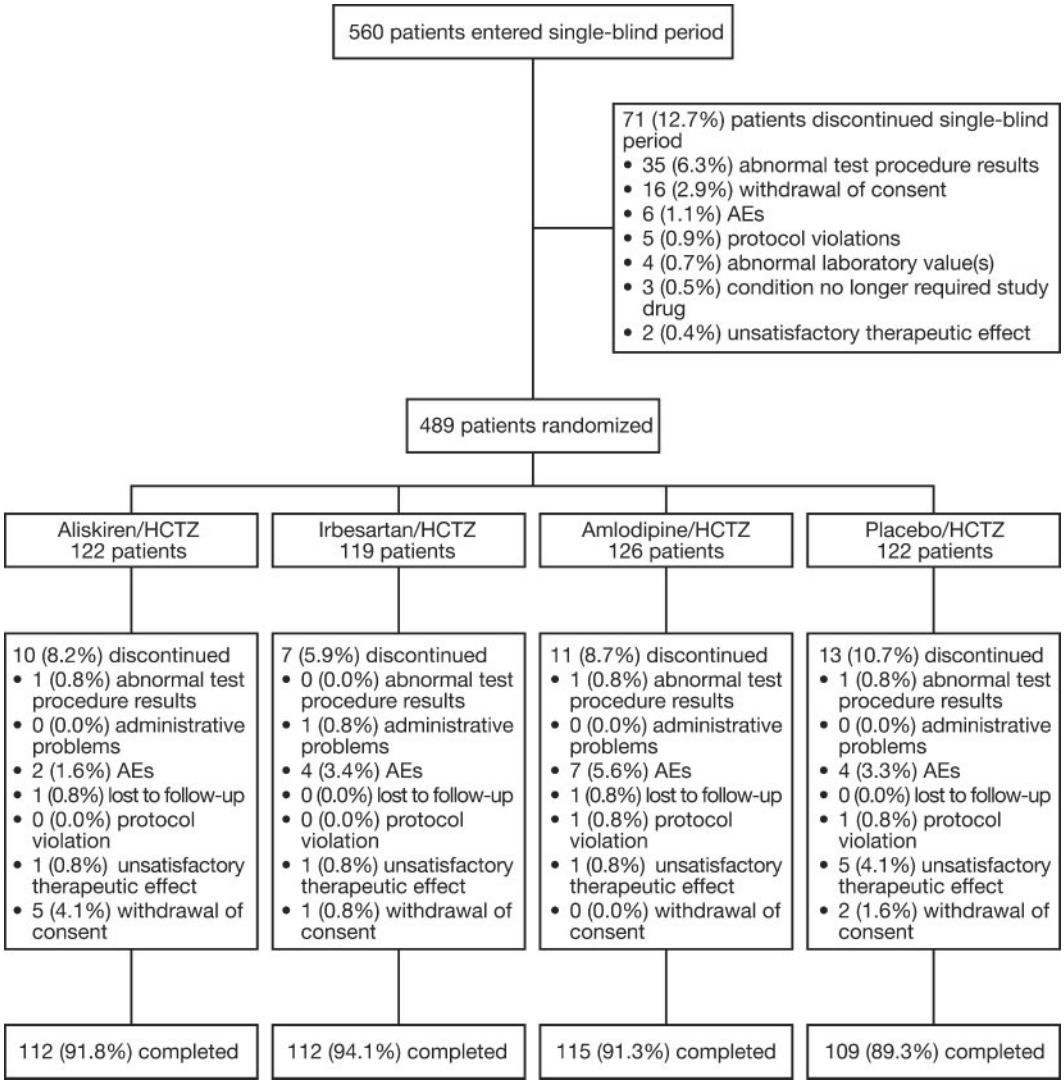

Figure 2. Patient flow diagram. AE indicates adverse event.

observed with amlodipine/HCTZ (56.6% versus 45.1%; $P=0.052$).

PRA

Pretreatment geometric mean PRA in randomly assigned patients was 0.60 ng/mL per hour (95% CI: 0.51 to 0.71; n=176). PRA was significantly increased ($P<0.05$) by single-blind HCTZ treatment. Combination with aliskiren in the double-blind treatment period neutralized this increase and led to an overall significant reduction in PRA ($P<0.05$) compared with the pretreatment baseline (Figure 5). By contrast, combination of HCTZ with irbesartan or amlodipine led to further significant increases in PRA.

Safety and Tolerability

All of the study treatments were generally well tolerated. Overall, 195 (39.9%) of the 489 patients in the safety population experienced adverse events (Table 3), which were mostly mild and transient in nature. Amlodipine/HCTZ was associated with a higher incidence of adverse events (45.2%) than the other treatment groups (36.1% to 39.3%), largely because of a higher rate of peripheral edema in this group (14 patients, compared with 4 patients in the other groups combined). Four of these cases of peripheral edema caused patients to discontinue amlodipine/HCTZ, accounting for the higher overall rate of discontinuations because of adverse events in this treatment group. The other most commonly observed adverse events were nasopharyngitis, headache, dizziness, and back pain. Diarrhea was reported by 3 patients receiving placebo/HCTZ and 1 patient on amlodipine/HCTZ; there were no reports of diarrhea with aliskiren/HCTZ or irbesartan/HCTZ.

The incidence of serious adverse events was low and similar across treatment groups; the only serious adverse event suspected to be related to study treatment was a case of peripheral edema in a patient receiving amlodipine/HCTZ, and this event was resolved after discontinuation of study drugs. There were no deaths during the study.

No patient discontinued study treatment because of abnormal laboratory values. The proportion of patients exhibiting serum potassium <3.5 mmol/L was twice as high with amlodipine/HCTZ compared with the other treatment groups

TABLE 1. Patient Baseline and Demographic Characteristics (Randomized Population)

Characteristic	Aliskiren/HCTZ (n=122)	Irbesartan/HCTZ (n=119)	Amlodipine/HCTZ (n=126)	HCTZ (n=122)
Age, y	53.1±11.9	53.0±11.0	55.2±11.9	55.2±12.3
≥65 years, n (%)	21 (17.2)	20 (16.8)	28 (22.2)	32 (26.2)
≥75 years, n (%)	4 (3.3)	1 (0.8)	6 (4.8)	8 (6.6)
Gender, male/female	60/62	48/71	53/73	52/70
Race, n (%)				
White	122 (100.0)	118 (99.2)	126 (100.0)	121 (99.2)
Other	0	1 (0.8)	0	1 (0.8)
Weight, kg	98.7±17.9	96.0±14.9	96.7±16.9	95.5±14.3
BMI, kg/m^2	34.8±5.2	34.3±4.7	34.5±4.1	34.0±4.1
Duration of hypertension, y	8.5±8.1	8.2±7.7	9.4±8.7	8.7±8.5
Metabolic syndrome, n (%)*	89 (73.0)	85 (71.4)	82 (65.1)	75 (61.5)
Current smoker, n (%)	18 (14.8)	20 (16.8)	30 (23.8)	24 (19.7)
Prior medications, n (%)				
ACE inhibitor	22 (18.0)	25 (21.0)	23 (18.3)	15 (12.3)
β-Blocker	12 (9.8)	12 (10.1)	11 (8.7)	11 (9.0)
Dihydropyridine CCB	9 (7.4)	10 (8.4)	10 (7.9)	11 (9.0)
Thiazide diuretic	5 (4.1)	8 (6.7)	9 (7.1)	7 (5.7)
ARB	10 (8.2)	2 (1.7)	7 (5.6)	8 (6.6)
ACE inhibitor/diuretic combination	5 (4.1)	6 (5.0)	10 (7.9)	4 (3.3)
ARB/diuretic combination	2 (1.6)	5 (4.2)	5 (4.0)	7 (5.7)
msDBP, mm Hg	96.8±4.9	96.6±4.4	96.7±5.0	97.2±4.6
msSBP, mm Hg	149.4±11.6	149.1±13.4	149.8±11.5	149.5±11.3

Baseline msDBP and msSBP were evaluated at baseline of the double-blind treatment period after the single-blind HCTZ run-in period. Data are expressed as mean±SD unless otherwise stated.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

*Metabolic syndrome was defined as any 3 of the following, according to National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria[19]: waist circumference >102 cm for men or >88 cm for women; triglycerides ≥150 mg/dL (≥1.69 mmol/L); high-density lipoprotein cholesterol <40 mg/dL (<1.04 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women; BP ≥130/85 mm Hg; and fasting glucose ≥110 mg/dL (≥6.1 mmol/L).

(Table 3). The rate of serum potassium elevations to >5.5 mmol/L was highest with aliskiren/HCTZ (5 patients, 4.1%). Two of these patients exhibited serum potassium ≥6.0 mmol/L; no further action was taken for either patient, because the first (abnormal value on day 28) discontinued the study because of unsatisfactory therapeutic effect, whereas the second patient exhibited high potassium levels at the final week 12 visit.

None of the study treatments resulted in weight gain. Compared with values measured at screening, aliskiren/HCTZ was associated with a 0.9±3.0 kg reduction (n=116) in body weight at end point compared with reductions of 0.4±2.7 kg with HCTZ alone (n=112), 0.3±2.6 kg with irbesartan/HCTZ (n=114), and 0.1±3.3 kg with amlodipine/HCTZ (n=121).

Discussion

This study is the first to investigate the use of other antihypertensive therapies in combination with HCTZ in a population of obese patients with hypertension who have failed to achieve BP control with HCTZ monotherapy. The addition of aliskiren (150 mg) to treatment with HCTZ (25 mg) for 4 weeks provided a significant additional BP reduction (msSBP/DBP) of 4.4/2.5 mm Hg compared with continuing treatment with HCTZ alone, and increasing the dose of aliskiren to 300 mg for 4 weeks increased the treatment difference to 7.2/4.0 mm Hg. The additional BP reduction provided by combining aliskiren with HCTZ treatment almost doubled the rate of BP control in obese hypertensive patients at 12 weeks (58.4% versus 33.3% with HCTZ alone). The antihypertensive effects of aliskiren were similar to those observed with irbesartan and amlodipine.

Combination with aliskiren suppressed the increase in renin system activity (PRA) caused by HCTZ, whereas irbesartan and amlodipine increased PRA further. Our results are consistent with the findings of an 8-week, placebo-controlled multifactorial trial of aliskiren/HCTZ combinations in patients with mild-to-moderate hypertension (of whom ≈40% were obese) [12] and confirm the excellent antihypertensive efficacy of aliskiren in combination with HCTZ.

Few studies have been conducted specifically in patients with obesity and hypertension (and none with the same design as the present study), and so direct comparisons of the efficacy of aliskiren with previous studies in this patient population are difficult. Baseline characteristics of obese

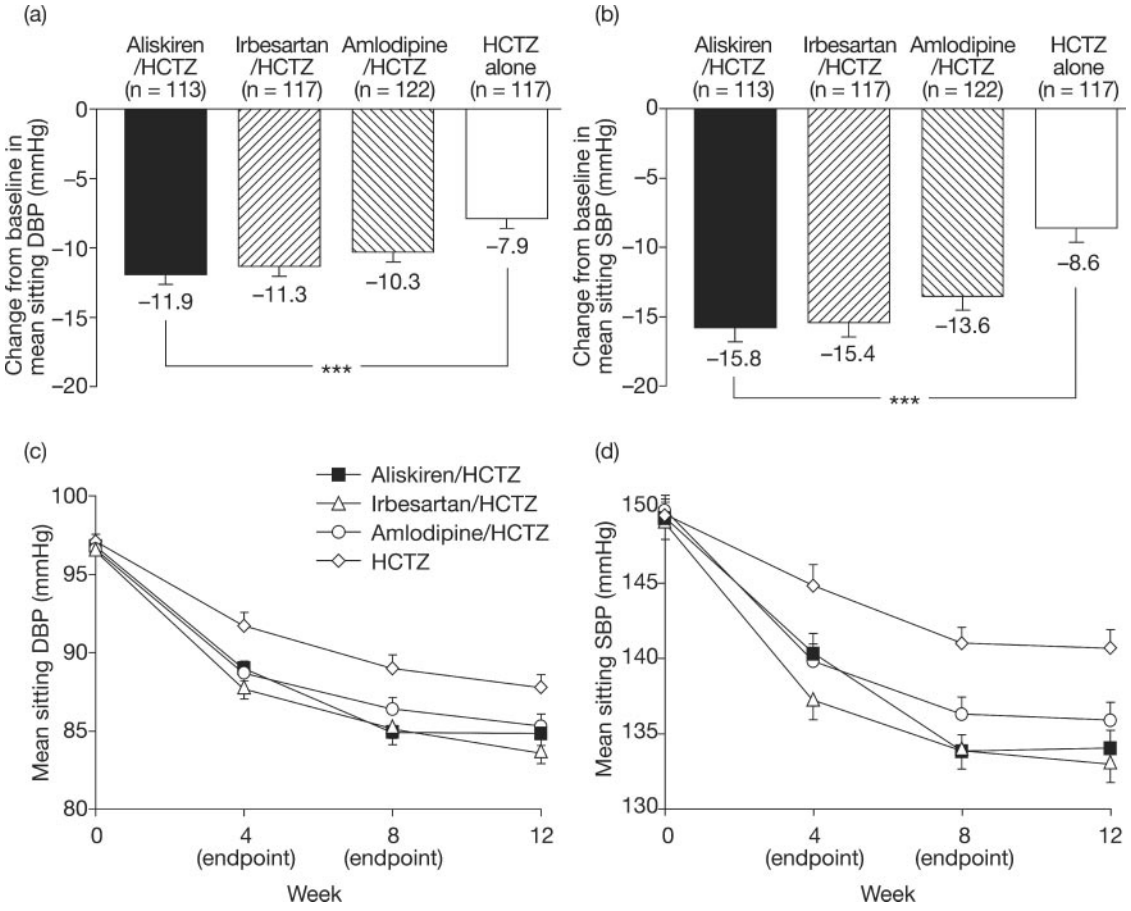

Figure 3. Changes from baseline in (a) msDBP and (b) msSBP at week 8 end point and summary statistics for (c) msDBP and (d) msSBP throughout the double-blind period (ITT population). a and b, Mean changes from baseline at week 8 end point with aliskiren/HCTZ (■), irbesartan/HCTZ (▨), amlodipine/HCTZ (▧), or HCTZ alone (□). c and d, Summary statistics for msDBP and msSBP during double-blind treatment with aliskiren/HCTZ (■), irbesartan/HCTZ (△), amlodipine/HCTZ (○), or HCTZ alone (◇). Data are presented as least-squares mean±SEM. ***$P<0.0001$ in pairwise comparisons.

patients with hypertension in the present study resembled the profile observed in previous clinical studies.[8,20,21] However, mean BMI at baseline in the present study (34.4 kg/m^2) was higher than in previous studies and suggests that close to half of the patients enrolled had BMI ≥35 kg/m^2, that is, obesity grade 2 (BMI: 35 to 39.9 kg/m^2) or grade 3 (BMI: ≥40 kg/m^2). Nevertheless, BP control rates with aliskiren/HCTZ compare favorably with the control rates of 34% and 38% observed with valsartan and the β-blocker atenolol, respectively (with addition of 12.5 to 25 mg of HCTZ as

TABLE 2. Between-Group Comparisons of Changes From Baseline in msDBP and msSBP at Week 8 End Point (ITT Population)

Treatment Group	N	LSM Change From Baseline, mm Hg	LSM Difference Compared With Aliskiren/HCTZ (95% CI), mm Hg	*P*
msDBP				
Aliskiren 300 mg/HCTZ 25 mg	113	−11.91±0.74		
Irbesartan 300 mg/HCTZ 25 mg	117	−11.33±0.72	−0.57 (−2.58 to 1.43)	0.576
Amlodipine 10 mg/HCTZ 25 mg	122	−10.30±0.71	−1.60 (−3.59 to 0.38)	0.114
HCTZ 25 mg	117	−7.89±0.73	−4.02 (−6.02 to −2.01)	<0.0001
msSBP				
Aliskiren 300 mg/HCTZ 25 mg	113	−15.79±1.01		
Irbesartan 300 mg/HCTZ 25 mg	117	−15.44±1.00	−0.35 (−3.11 to 2.40)	0.801
Amlodipine 10 mg/HCTZ 25 mg	122	−13.55±0.98	−2.24 (−4.97 to 0.49)	0.107
HCTZ 25 mg	117	−8.62±1.00	−7.17 (−9.93 to −4.41)	<0.0001

LSM indicates least-squares mean. Values are shown as least-squares mean±SEM unless otherwise stated. Statistical comparisons were made using an ANCOVA model as described in the Methods.

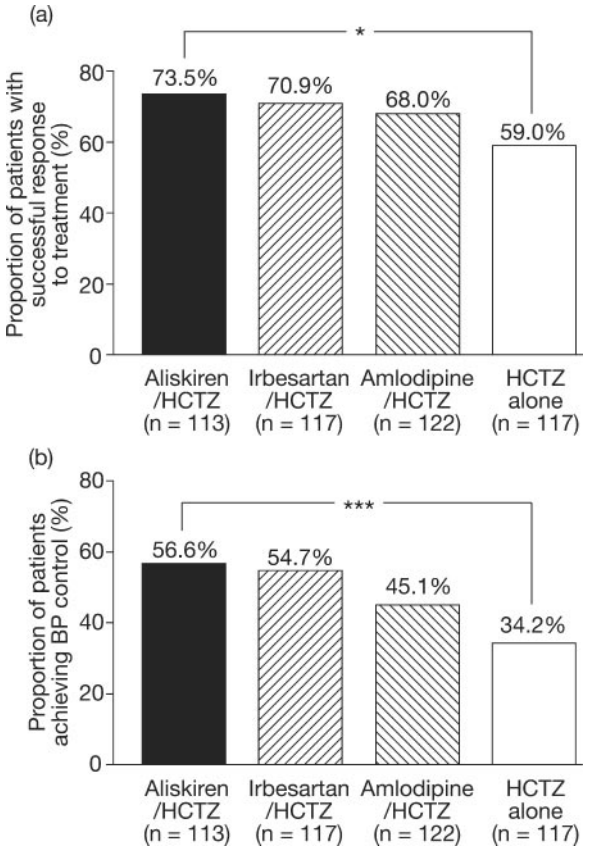

Figure 4. Proportion of patients exhibiting (a) successful msDBP response and (b) BP control at week 8 end point (ITT population). Graph shows responder rates (msDBP <90 mm Hg or ≥10 mm Hg reduction) and BP control rates (BP <140/90 mm Hg) at week 8 end point with aliskiren/HCTZ (■), irbesartan/HCTZ (▨), amlodipine/HCTZ (▧), or HCTZ alone (□). Data are presented as the percentage of patients with successful BP response or BP control. *P<0.05; ***P=0.0005.

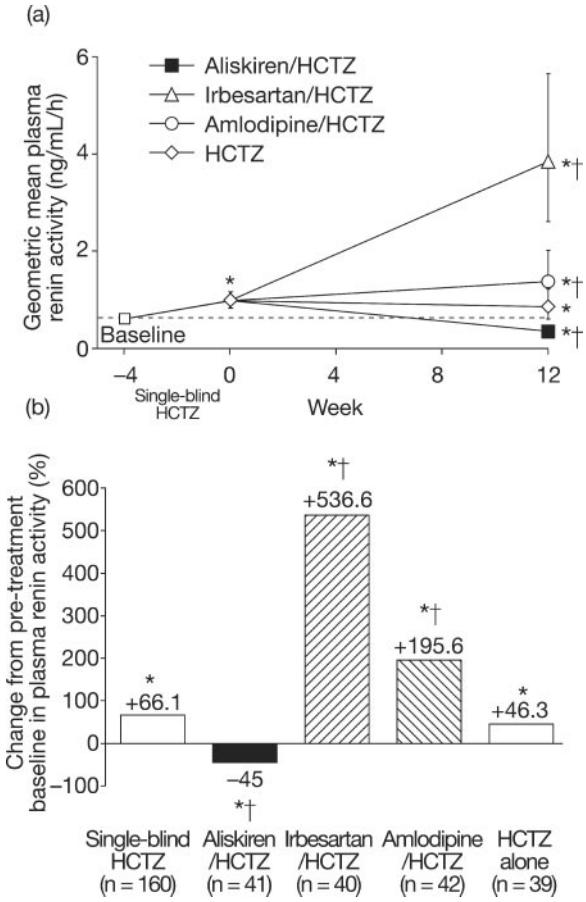

Figure 5. Geometric mean PRA (ITT population) (a) throughout study and (b) mean percentage change in PRA from pretreatment baseline (week −4) after treatment with single-blind HCTZ (week 0) and double-blind treatment (week 12). Graph shows (a) geometric mean PRA (horizontal dashed line denotes pretreatment baseline PRA) and (b) percentage change in PRA from pretreatment baseline with single-blind HCTZ (◇/□), aliskiren/HCTZ (■/■), irbesartan/HCTZ (△/▨), amlodipine/HCTZ (○/▧), or HCTZ alone (◇/□). Geometric mean PRAs at pretreatment baseline and after treatment with single-blind HCTZ were pooled for patients across all of the randomization groups. Percentage change in geometric mean PRA was compared for matched data in patients within each double-blind randomized group; geometric mean PRA values at pretreatment baseline (week −4) were 0.60, 0.62, 0.54, and 0.65 ng/mL per hour for patients who were subsequently randomly assigned to aliskiren/HCTZ, irbesartan/HCTZ, amlodipine/HCTZ, or HCTZ alone, respectively, whereas geometric mean PRA values after 4 weeks of single-blind HCTZ (week 0) were 1.00, 1.06, 0.81, and 1.14 ng/mL per hour, respectively. *P<0.05 vs pretreatment baseline (week −4) and †P<0.05 vs single-blind HCTZ (week 0), determined by nonoverlapping 95% CI of geometric mean ratio of change from baseline in PRA for patients in the respective double-blind, randomly assigned group.

required) in a recent 13-week study in 132 obese patients with hypertension.[8]

The observation that treatment with HCTZ (25 mg) alone for 12 weeks achieved BP control in only one third of obese patients with hypertension is similar to the control rate of 43% observed with 12.5 to 50 mg of HCTZ daily in the Treatment in Obese Patients With Hypertension Study.[20] In patients randomly assigned to receive HCTZ alone, further BP reductions from baseline were observed during double-blind treatment, although these patients continued the same HCTZ dose. Some of the additional BP reduction may be attributed to a placebo effect. However, these results are likely to reflect, at least in part, the relatively slow response to HCTZ treatment in patients with obesity. Indeed, the Treatment in Obese Patients With Hypertension Study showed significantly smaller DBP reductions with HCTZ compared with the angiotensin-converting enzyme inhibitor lisinopril after 4 or 8 weeks of treatment, although responses at 12 weeks were similar.[20]

The combination of aliskiren with ongoing HCTZ treatment was well tolerated and was not associated with a notably higher incidence of adverse events than treatment with HCTZ alone. Amlodipine/HCTZ was associated with a markedly higher rate of peripheral edema compared with all of the other treatment groups. Peripheral edema is a common adverse effect of higher doses of amlodipine, such as the 10-mg dose used in the present study,[22] and the fact that 4 patients discontinued amlodipine/HCTZ as a result of edema is consistent with clinical experience with this drug.[23] The incidence of laboratory abnormalities was generally low across the 4 treatment groups. Hypokalemia is a known adverse effect of HCTZ treatment, but the incidence of reductions in serum potassium to <3.5 mmol/L was higher

TABLE 3. Safety and Tolerability of Study Treatments (Safety Population)

	Aliskiren/HCTZ (n=122)	Irbesartan/HCTZ (n=119)	Amlodipine/HCTZ (n=126)	HCTZ (n=122)
Adverse event				
Any adverse event	48 (39.3)	43 (36.1)	57 (45.2)	47 (38.5)
Discontinuations due to adverse events	2 (1.6)	4 (3.4)	7 (5.6)	4 (3.3)
Serious adverse events	2 (1.6)	3 (2.5)	4 (3.2)	4 (3.3)
Adverse events occurring in ≥2% of patients in any treatment group				
Nasopharyngitis	10 (8.2)	6 (5.0)	7 (5.6)	5 (4.1)
Headache	5 (4.1)	3 (2.5)	9 (7.1)	4 (3.3)
Dizziness	4 (3.3)	3 (2.5)	1 (0.8)	2 (1.6)
Peripheral edema	1 (0.8)	1 (0.8)	14 (11.1)	2 (1.6)
Back pain	1 (0.8)	2 (1.7)	5 (4.0)	5 (4.1)
Clinically notable changes in laboratory values				
BUN, >14.28 mmol/L	0 (0.0)	3 (2.5)	0 (0.0)	1 (0.8)
Creatinine, >176.8 μmol/L	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Potassium				
<3.5 mmol/L	6 (4.9)	3 (2.5)	13 (10.3)	5 (4.1)
>5.5 mmol/L	5 (4.1)	3 (2.5)	1 (0.8)	3 (2.5)
≥6.0 mmol/L	2 (1.6)	0 (0.0)	1 (0.8)	1 (0.8)

BUN indicates blood urea nitrogen. Values are presented as the number (%) of patients.

during combination treatment with amlodipine. Reductions in serum potassium levels have been observed previously in a small study of the combination of amlodipine (5 mg) with the diuretic bendrofluazide (5 mg) in nonobese patients with hypertension, but these were attributed solely to the effects of the diuretic.[24] Increases in serum potassium (a known effect of renin system blocking agents) were more common with aliskiren/HCTZ than the other treatment groups. Given that the rate of serum potassium elevation with placebo/HCTZ was similar to that observed with irbesartan/HCTZ, sampling hemolysis may explain some of these abnormalities. In any case, serum potassium elevations with aliskiren/HCTZ were not associated with adverse events, and routine clinical monitoring in patients receiving thiazide diuretic treatment should be sufficient to detect and address them. None of the treatments were associated with weight gain.

Similar BP reductions were observed with a combination of aliskiren, irbesartan, or amlodipine with HCTZ in this study. Early, small studies suggested that dihydropyridine calcium channel blockers were less effective for the treatment of obesity-associated hypertension.[25] Furthermore, they could further increase sympathetic nervous system activity[26,27] (a known factor in weight gain-associated BP elevation).[28] Our results are consistent with more recent studies indicating that calcium channel blockers provide similar BP reductions to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in obese patients with hypertension.[21,26] However, the marked increase in the incidence of peripheral edema observed with amlodipine/HCTZ in the present study suggests that tolerability issues may limit the usefulness of calcium channel blockers in obesity-associated hypertension.

Perspectives

This study demonstrates that once-daily combination treatment with the direct renin inhibitor aliskiren represents a highly effective and well-tolerated therapeutic option for obese patients with hypertension who fail to achieve BP control with first-line thiazide diuretic treatment (as recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 guidelines). Combination of aliskiren with HCTZ (25 mg) provided significant additional BP reductions compared with HCTZ alone, and the aliskiren/HCTZ combination enabled more than half of patients to achieve BP control (<140/90 mm Hg) after 8 weeks of treatment. The effects of aliskiren were similar to those obtained by combination treatment with the angiotensin receptor blocker irbesartan or the calcium channel blocker amlodipine. Aliskiren showed similar excellent tolerability to irbesartan and was not associated with the increased rate of peripheral edema observed with amlodipine. Aliskiren also provided effective renin system control (PRA reduction) in combination with HCTZ, whereas irbesartan, amlodipine, and HCTZ alone all increased PRA. Further studies are required to investigate the potential organ protective benefits of improved renin system control with aliskiren.

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