Original Paper

Combination Therapy With Various Combinations of Aliskiren, Valsartan, and Hydrochlorothiazide in Hypertensive Patients Not Adequately Responsive to Hydrochlorothiazide Alone

Helmut Geiger, MD;[1] Elizabeth Barranco, MD;[2] Manuel Gorostidi, MD;[3] Addison Taylor, MD;[4] Xiaoli Zhang, MD, MS;[5] Zhihua Xiang, PhD;[5] Jack Zhang, MD, PhD[5]

This study investigated the efficacy and safety of several different multi-drug regimens including aliskiren, valsartan, and hydrochlorothiazide (HCTZ) in patients not adequately responsive to HCTZ as monotherapy. After 4 weeks of HCTZ treatment, patients (N=641) whose diastolic blood pressure (DBP) was ≥95 mm Hg were treated for 8 weeks with either aliskiren/valsartan/HCTZ, aliskiren/HCTZ, valsartan/HCTZ, or HCTZ alone. The primary efficacy variable was change in DBP from baseline to week 8 end point. The aliskiren/valsartan/HCTZ combination produced statistically significant additional reductions in systolic blood pressure (SBP)/DBP when compared with other groups. At week 8 end point, reductions in SBP/DBP in the respective treatment groups were 22/16, 15/11, 18/14, or 6/6 mm Hg. Aliskiren/valsartan/HCTZ produced significantly better blood pressure control (SBP/DBP <140/90 mm Hg; 66.7%) compared with other treatment groups (20.5%–48.7%). The safety profile of aliskiren/valsartan/HCTZ was similar to the 2-drug combinations, with a greater blood pressure–lowering effect in patients who had not responded to HCTZ monotherapy. J Clin Hypertens (Greenwich). *2009;11:324–332.* ©*2009 Wiley Periodicals, Inc.*

From the Johann-W. Goethe Universität, Zentrum für Innere Medizin, Funktionsbereich Nephrologie, Frankfurt, Germany;[1] Ponce School of Medicine, CAIMED Center, Ponce, Puerto Rico;[2] Sección de Nefrología, Hospital San Agustín, Avilés, Spain;[3] Baylor College of Medicine, Houston, TX;[4] and Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ[5]

Address for correspondence:
Helmut Geiger, MD, Johann-W. Goethe Universität, Zentrum für Innere Medizin, Funktionsbereich Nephrologie, Theodor-Stern-Kai 7, Frankfurt 60590, Germany
E-mail: h.geiger@em.uni-frankfurt.de
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Thiazide diuretics such as hydrochlorothiazide (HCTZ) are recommended as initial antihypertensive treatment in both the United States[1] and Europe.[2] Many patients, however, may need multiple antihypertensive agents to achieve the desired blood pressure (BP) level, especially those with comorbidities and BPs >160/100 mm Hg. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) suggested 2 medications as initial therapy in many patients in this group. For patients with an unsatisfactory BP response to HCTZ, the addition of

an agent acting on the renin-angiotensin system (RAS) is a commonly used therapeutic strategy, given that diuretics activate the RAS through volume depletion. Aliskiren, an orally effective direct renin inhibitor (DRI), has been shown to be efficacious and safe in the treatment of hypertension when used alone or in combination with other antihypertensive agents, including HCTZ.[3] In a study in obese hypertensive patients (N=489) not adequately responsive to 4 weeks of HCTZ (25 mg) treatment, persons who received aliskiren as an add-on to HCTZ experienced clinically and statistically significant greater BP reduction compared with those continuing to take HCTZ alone.[4] These results were expected since a number of studies have demonstrated an increased BP response to a diuretic and an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).[5,6]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[7] indicated that after 5 years of follow-up, 27% of patients required ≥3 drugs to achieve BP control. In high-risk hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure–Lowering Arm (ASCOT-BPLA),[8] after a median follow-up of 5.5 years, the average number of antihypertensive agents used to reach target BP level was >2.2, indicating that a large number of patients needed ≥3 drugs to reach goal BPs. Although several studies have shown that a proportion of patients require >2 drugs for adequate BP control, there are no published data exploring the therapeutic strategy of a combination of 3 medications.

The present study evaluated the efficacy and safety of triple-drug therapy with 2 RAS-blocking agents (aliskiren and valsartan) added simultaneously to HCTZ in hypertensive patients who were not adequately responsive to HCTZ alone.

PATIENTS AND METHODS

Study Population

Outpatients (male/female aged 18 years and older) with mild to moderate essential hypertension were enrolled from 112 centers (Germany, 47; Spain, 17; the United States, 48). Patients were taking antihypertensive agents before enrollment. These were stopped prior to the start of a single-blind HCTZ run-in period.

All patients with a diastolic BP (DBP) ≥95 mm Hg after 4 weeks of HCTZ treatment were included in an 8-week double-blind treatment program. The major exclusion criteria before the HCTZ run-in period were severe hypertension (DBP ≥110 mm Hg and/or systolic BP [SBP] ≥180 mm Hg), secondary hypertension, severe cardiovascular/cerebrovascular diseases, or severe life-threatening conditions. Patients with serum potassium ≥5.3 mEq/L and serum creatinine >1.5 times the upper limit of normal were also excluded.

The study was conducted according to good clinical practice guidelines and in compliance with the Declaration of Helsinki (2002). The study protocol received approval from the local or central ethical review boards. All patients provided written informed consent before entering the study.

Study Design

This was a randomized, double-blind, parallel-group, active-control, dose-escalation study. Following 4-week, single-blind HCTZ treatment (12.5 mg for 1 week; 25 mg for 3 weeks), qualified patients (DBP ≥95 mm Hg) were randomized to the equal ratio to receive treatment of aliskiren/valsartan/HCTZ (150/160/25 mg for 4 weeks; 300/320/25 mg for another 4 weeks), aliskiren/HCTZ (150/25 mg for 4 weeks; 300/25 mg for another 4 weeks), valsartan/HCTZ (160/25 mg for 4 weeks; 320/25 mg for another 4 weeks), or HCTZ (25 mg for 8 weeks) (Figure 1). Treatment in patients who experienced SBP ≥180 mm Hg or DBP ≥110 mm Hg at any time during the study was discontinued and appropriate therapy was instituted.

Efficacy and Safety Assessments

The primary efficacy variable was the change in DBP from baseline to the week 8 end point, and the primary objective was the comparison at the week 8 end point for the triple combination of aliskiren/valsartan/HCTZ (300/320/25 mg) with both double combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg).

The secondary efficacy variables included changes from baseline to week 8 end point in SBP, changes in DBP and SBP at week 4 (low-dose therapy period), and the proportion of patients achieving BP control (SBP/DBP <140/90 mm Hg). Exploratory efficacy variables included the change from baseline to week 8 end point in plasma renin activity (PRA) and plasma renin concentration (PRC).

BP was measured using an automatic BP monitor at trough (24±3 hours post-dose) during all study visits. Three sitting BP measurements were taken at 1- to 2-minute intervals, and the average

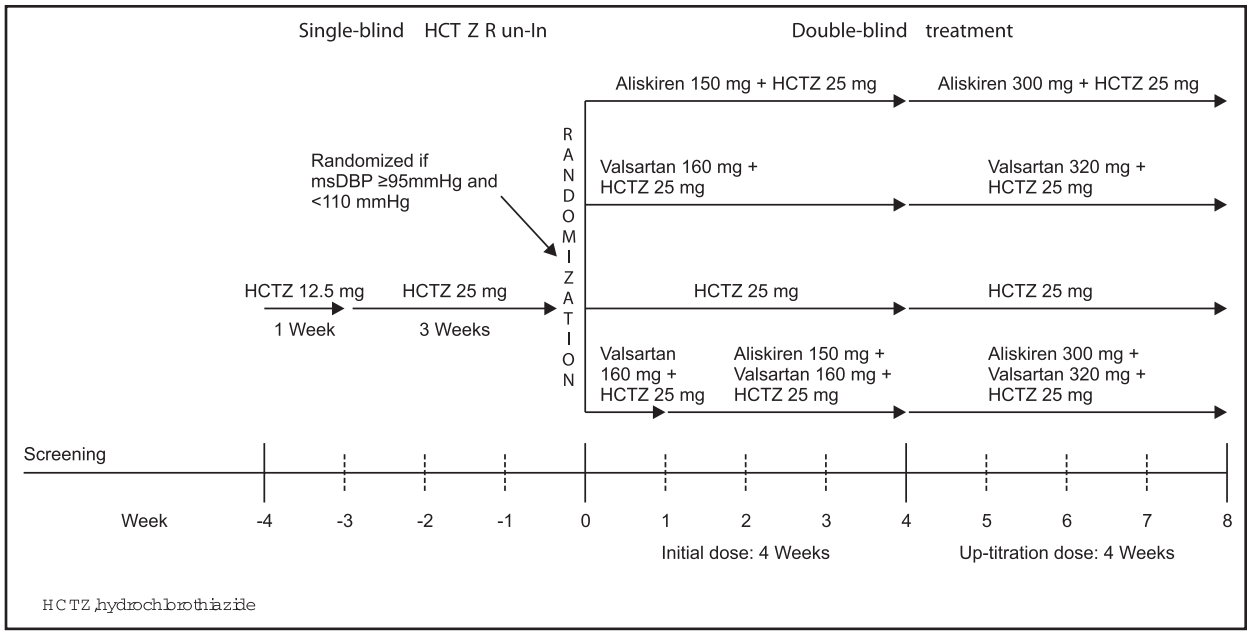

Figure 1. Study design.

of the 3 readings was taken as the mean BP for that visit.

The safety assessments consisted of regular monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs) (with their duration, intensity, relationship to study drug), vital signs, physical examinations, and laboratory evaluations. A set of laboratory parameters that has potentially clinical significance associated with the treatment with HCTZ or RAS-blocking agents were prespecified in the study protocol, including serum potassium <3.5 or >5.5 mEq/L, serum urea nitrogen >40.05 mg/dL, and serum creatinine >2.0 mg/dL.

Biomarker Assays

After the single-blind HCTZ run-in period, PRC and PRA were obtained at baseline and at week 8 in the subset of patients (HCTZ group: n=43 [28%]; aliskiren/HCTZ group: n=47 [29%]; valsartan/HCTZ group: n=42 [27%]; aliskiren/valsartan/HCTZ group: n=52 [31%]). PRA and PRC were measured by radioimmunoassay kits.

Statistical Analyses

A sample size of 560 (140 per arm) completed patients was targeted. Assuming a drop-out rate of 10%, 624 patients (156 per arm) were planned for randomization with an equal randomization ratio 1:1:1:1. Using the population of completed patients, a sample size of 560 (140 per arm) would have 80% statistical power to detect a difference of 3.0 mm Hg for both combination and individual comparisons.

The primary analysis was performed on the intent-to-treat (ITT) population defined as all randomized patients who received at least 1 dose of the study drug during the double-blind period and had a baseline and at least 1 post-baseline assessment of the primary efficacy variable (change in DBP from baseline).

The primary efficacy variable (at week 8 end point) was analyzed using an analysis of covariance (ANCOVA) model with treatment and region as factors and with baseline as a covariate. The changes in DBP and SBP from baseline to the week 4 end point and at week 8 and changes in SBP from baseline to the week 8 end point were also analyzed for the ITT population using the ANCOVA model.

The hypothesis testing was performed using a 2-sided test at a significance level of .05 based on the primary ANCOVA model. In addition, for the differences between aliskiren/valsartan/HCTZ combination and aliskiren/HCTZ and valsartan/HCTZ combinations, the 95% confidence interval was also provided.

The proportion of responders (DBP <90 mm Hg or reduction of DBP ≥10 mm Hg from baseline) in each treatment was compared for aliskiren/valsartan/HCTZ combination with aliskiren/HCTZ and valsartan/HCTZ combinations using a logistic regression model, with treatment

Table I. Baseline and Demographic Characteristics by Treatment Group (ITT Population)

Variables	Aliskiren/Valsartan/HCTZ (n=168)	Aliskiren/HCTZ (n=166)	Valsartan/HCTZ (n=155)	HCTZ (n=152)	*P* Value
Demographic variables					
Age, y					
No.	168	166	155	152	.12
Mean (SD)	52.9 (10.83)	52.3 (10.90)	55.0 (11.40)	52.6 (9.93)	
Age group, y					
<65	141	143	123	136	.09
≥65	27	23	32	16	
Sex (F/M)	77/91	74/92	67/88	58/94	.53
Race, No. (%)					
Caucasian	147 (87.5)	141 (84.9)	135 (87.1)	131 (86.2)	.85
Black	15 (8.9)	16 (9.6)	14 (9.0)	13 (8.6)	
Asian	1 (0.6)	5 (3.0)	4 (2.6)	3 (2.0)	
Native American/other	5 (3.0)	4 (2.4)	2 (1.3)	5 (3.3)	
Body mass index, kg/m^2					
No.	166	166	154	152	.72
Mean (SD)	31.9 (6.21)	31.3 (6.28)	31.3 (5.85)	31.8 (6.13)	
Duration of hypertension history, y					
No.	162	161	151	149	–
Mean (SD)	8.6 (8.06)	7.8 (7.38)	9.2 (8.96)	8.0 (7.42)	
Diabetic status, No. (%)	18 (10.7)	20 (12)	19 (12.3)	21 (13.8)	–
Baseline variables					
DBP, mm Hg					
No.	168	166	154	152	.27
Mean (SD)	99.2 (3.70)	99.3 (4.10)	99.9 (3.97)	99.9 (4.33)	
SBP, mm Hg					
No.	168	166	154	152	.01
Mean (SD)	152.7 (11.64)	153.3 (12.68)	156.7 (12.49)	154.1 (12.61)	

Abbreviations: DBP, diastolic blood pressure; F, female; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; M, male; SBP, systolic blood pressure; SD, standard deviation.

and region as the factors and baseline DBP as a covariate.

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

The demographics and baseline characteristics were comparable for all treatment groups. Fifty-seven percent were male. The mean age was 53.2 years (approximately 15% were 65 years or older and 3% were 75 years or older) (Table I). Of the 1249 patients who were enrolled in the 4-week single-blind, HCTZ treatment, 641 (51.3%) completed the treatment and were included in the 8-week double-blind treatment.

Of the 641 patients who were randomized, 168 were included in the aliskiren/valsartan/HCTZ group, 166 in the aliskiren/HCTZ group, 155 in the valsartan/HCTZ group, and 152 in the HCTZ group. Baseline DBP after HCTZ run-in ranged from 99.2 to 99.9 mm Hg among treatment groups; 52% of the patients had an SBP ≥160 mm Hg and/or DBP ≥100 mm Hg. A total of 583 patients (91.0%) completed the study; the highest proportion were from the aliskiren/valsartan/HCTZ group (n=161, 95.8%) (Figure 2). Rates of premature discontinuation were the lowest in the aliskiren/valsartan/HCTZ group (n=7, 4.2%) and highest in the HCTZ group (n=19, 12.5%). This difference was primarily due to the higher rate of discontinuation due to unsatisfactory therapeutic effect in the HCTZ group. This difference was not statistically significant (*P*=.059) and, again, was not unexpected since the protocol design had determined that HCTZ alone was not effective in reducing BP to goal levels. No patient in the aliskiren/valsartan/HCTZ group discontinued treatment due to an unsatisfactory therapeutic effect (Figure 2). There were 3 patients in the aliskiren/HCTZ group and 3 patients in the valsartan/HCTZ group who

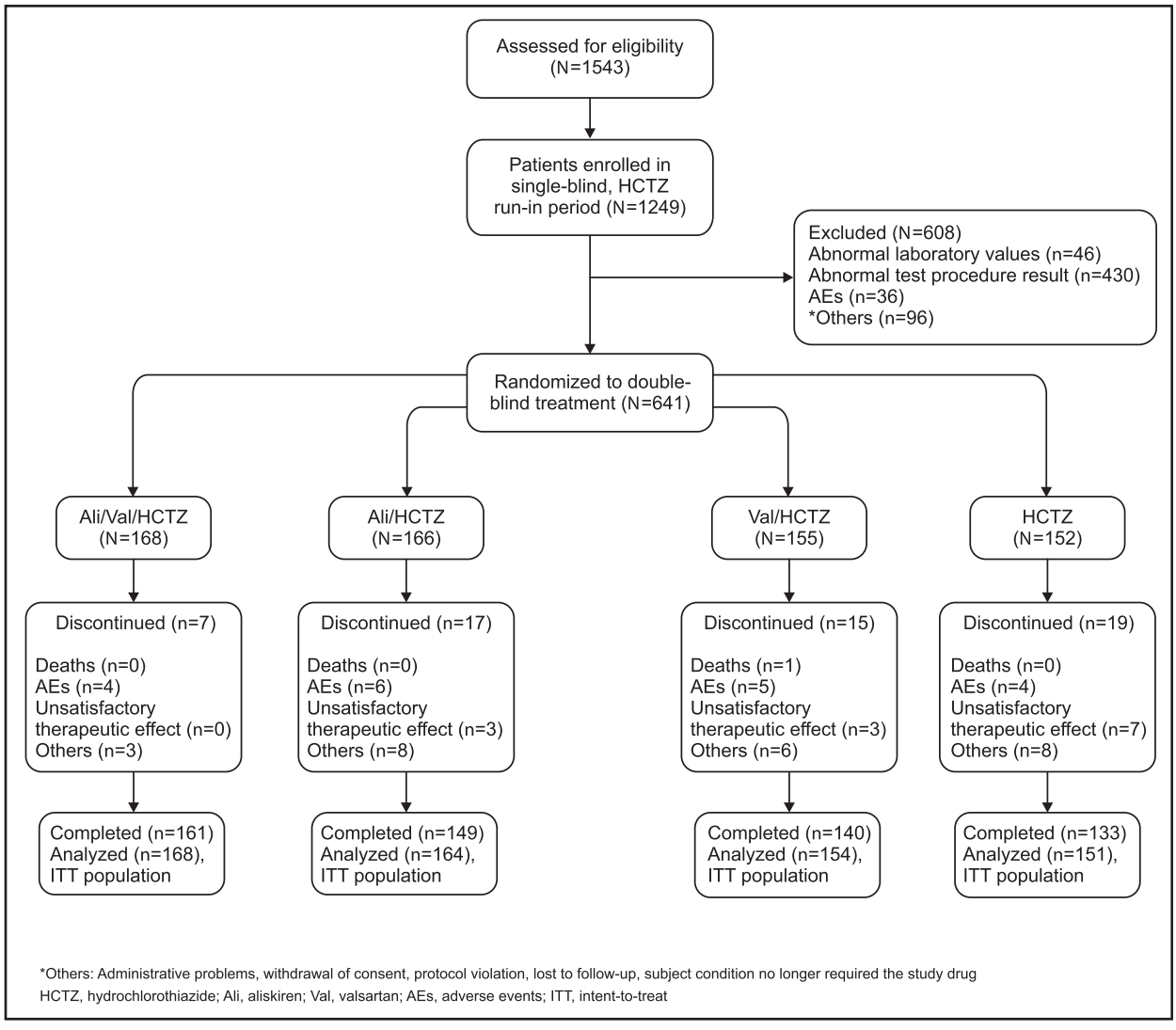

Figure 2. Patient disposition.

Table II. BP Change and Control Rates at Week 8 End Point

Treatment Group	No.	DBP (SE)	SBP (SE)	BP Control, (%)
HCTZ (25 mg)	151	−6 (0.70)	−6 (1.12)	31/151 (20.53)
Aliskiren/HCTZ (300/25 mg)	164	−11 (0.67)[a]	−15 (1.08)[a]	67/164 (40.85)[a]
Valsartan/HCTZ (320/25 mg)	154	−14 (0.70)[a]	−18 (1.12)[a]	75/154 (48.70)[a]
Aliskiren/valsartan/HCTZ (300/320/25 mg)	168	−16 (0.67)[a,b]	−22 (1.07)[a,b]	112/168 (66.67)[a,c]

Abbreviations: DBP, diastolic blood pressure (BP); HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; SE, standard error. [a]$P<.001$ vs HCTZ. [b]$P<.001$ vs aliskiren/HCTZ and $P<.01$ vs valsartan/HCTZ. [c]$P<.001$ vs aliskiren/HCTZ and valsartan/HCTZ.

discontinued treatment due to an unsatisfactory therapeutic effect.

Changes in SBP and DBP

At the week 8 end point, the aliskiren/valsartan/HCTZ group showed statistically significant greater reductions in both SBP and DBP compared with other groups, with additional SBP/DBP reductions of 7/5 mm Hg ($P<.0001$) when compared with the aliskiren/HCTZ group, 3/2 mm Hg ($P<.01$) compared with the valsartan/HCTZ group, and 15/10 mm Hg ($P<.001$) when

Table III. PRA and PRC Values at Baseline and Week 8 End Point (Subset Population)

Treatment Groups	No.	PRA, ng/mL/h		PRC, ng/L	
		Baseline	Week 8	Baseline	Week 8
HCTZ (25 mg)	43	1.52	1.32	17.01	12.06
Aliskiren/HCTZ (300/25 mg)	47	2.22	1.32	15.53	91.59
Valsartan/HCTZ (320/25 mg)	42	1.69	10.30	15.22	100.66
Aliskiren/valsartan/HCTZ (300/320/25 mg)	52	1.75	2.43	15.15	281.80

Abbreviations: HCTZ, hydrochlorothiazide; PRA, plasma renin activity; PRC, plasma renin concentration.

compared with the HCTZ group (Table II). As expected, both double-combination groups of aliskiren/HCTZ and valsartan/HCTZ demonstrated significantly greater SBP and DBP reductions compared with the HCTZ monotherapy group. As noted, valsartan was more effective than aliskiren in combination with HCTZ.

BP Control

The BP control rate (defined as SBP <140 mm Hg and DBP <90 mm Hg) at the week 8 end point in the aliskiren/valsartan/HCTZ (300/320/25 mg) group (66.7%) was significantly higher when compared with those in the respective doses of aliskiren/HCTZ (40.9%, $P<.001$), valsartan/HCTZ (48.7%, $P<.001$), and HCTZ (20.5%, $P<0.001$) groups (Table II). At week 4, a significantly greater BP control rate was also observed for the aliskiren/valsartan/HCTZ group at lower doses (150/160/25 mg) compared with the respective doses of the other groups: aliskiren/valsartan/HCTZ (300/320/25 mg) group (56%) compared with aliskiren/HCTZ (36.6%, $P<.05$), valsartan/HCTZ (42.2%, $P<.05$), and HCTZ (19.9%, $P<.01$) groups. Not surprisingly, both double-combination groups of aliskiren/HCTZ and valsartan/HCTZ demonstrated significantly greater BP control rates compared with the HCTZ monotherapy group both at week 8 and week 4 end points.

Markers of Renin System Activity

At week 8, PRC was essentially unchanged in the HCTZ group but was significantly increased in other groups, with the greatest increase observed in the aliskiren/valsartan/HCTZ group (Table III). A significant decrease in PRA from baseline was observed in the aliskiren/HCTZ group and a significant increase was observed in the valsartan/HCTZ group (geometric mean changes in PRA of 0.22 ng/mL/h and 4.80 ng/mL/h, respectively; $P<.001$ for both changes from baseline). In the HCTZ and aliskiren/valsartan/HCTZ groups, there was essentially no change in PRA (geometric mean changes in PRA of 0.96 ng/mL/h and 0.96 ng/mL/h, respectively; both $P>.75$). It is notable that despite a geometric mean change in renin of 15.64 ng/L in the aliskiren/valsartan/HCTZ group, PRA was not elevated. The baseline PRA and PRC were measured at the end of the 4-week single-blind HCTZ period. Therefore, the effect of HCTZ on PRA and PRC might have been stabilized with this initial therapy and no further changes after the 8-week additional HCTZ treatment was observed.

Safety

In the aliskiren/valsartan/HCTZ group, 62 patients (36.9%) reported at least 1 AE, which was similar or less than other groups; there were no deaths or SAEs (Table IV). The number of patients who discontinued the study prematurely due to AEs in the aliskiren/valsartan/HCTZ group was similar to other groups (Figure 2). In addition to AEs listed in Table IV, there was 1 AE of hypotension and 1 AE of orthostatic hypotension reported in the valsartan/HCTZ group (a combined incidence of 1.3%). Two patients (1.2%) had an AE of hypotension and none noted for orthostatic hypotension in the aliskiren/valsartan/HCTZ group. Syncope was reported as an AE in 2 patients (1.3%) in the valsartan/HCTZ group and in 2 patients (1 with syncope and 1 with vasovagal syncope, combined incidence of 1.2%) in the aliskiren/valsartan/HCTZ group.

One patient (0.6%) in the aliskiren/valsartan/HCTZ group and none in the other groups had hyperkalemia (defined as serum potassium 5.5 mEq/L at any post-baseline visit). However, repeat testing for this patient 2 weeks later showed a normal potassium value without discontinuation or dose reduction of the study drug. There were no symptoms/signs related to the elevated potassium level. The patient completed the study with the potassium value maintained within the normal range. None of the patients in the aliskiren/

Table IV. Safety and Tolerability of Study Treatments During the Double-Blind Treatment Period

	Aliskiren/Valsartan/ HCTZ (n=168)	Aliskiren/HCTZ (n=165)	Valsartan/HCTZ (n=154)	HCTZ (n=152)	*P* Value
AEs					
Any AE	62 (36.9)	60 (36.4)	72 (46.8)	64 (42.1)	.19
SAEs	0 (0)	1 (0.6)	5 (3.3)	1 (0.7)	.03
Frequent AEs					
(≥2% in any group)					
Dizziness	10 (6.0)	3 (1.8)	13 (8.4)	3 (2.0)	.01
Headache	5 (3.0)	4 (2.4)	9 (5.8)	8 (5.3)	.32
Fatigue	4 (2.4)	2 (1.2)	3 (1.9)	4 (2.6)	.81
Back pain	4 (2.4)	2 (1.2)	2 (1.3)	1 (0.7)	.61
Vertigo	4 (2.4)	2 (1.2)	1 (0.6)	0 (0.0)	.20
Nasopharyngitis	3 (1.8)	5 (3.0)	4 (2.6)	10 (6.6)	.1
Cough	3 (1.8)	2 (1.2)	4 (2.6)	2 (1.3)	.77
Hyperlipidemia	3 (1.8)	2 (1.2)	3 (1.9)	3 (2.0)	.95
Diarrhea	2 (1.2)	2 (1.2)	3 (1.9)	4 (2.6)	.72
Bronchitis	2 (1.2)	0 (0.0)	2 (1.3)	3 (2.0)	.39
Upper respiratory tract infection	1 (0.6)	3 (1.8)	2 (1.3)	3 (2.0)	.71
Eczema	1 (0.6)	1 (0.6)	1 (0.6)	3 (2.0)	.51
Edema peripheral	1 (0.6)	0 (0.0)	1 (0.6)	3 (2.0)	.24
Polyuria	0 (0.0)	4 (2.4)	2 (1.3)	0 (0.0)	.07
Prespecified clinically significant laboratory abnormalities					
Serum potassium, mEq/L					
<3.5	10 (6.0)	8 (5.0)	13 (8.5)	14 (9.3)	
>5.5	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Blood urea nitrogen, mg/dL					
>40.05	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	
Serum creatinine, mg/dL					
>2.0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Values are expressed as No. (%). Abbreviations: AEs, adverse events; HCTZ, hydrochlorothiazide; SAEs, serious adverse events.

valsartan/HCTZ group met the predefined criteria of a clinically significant increase in serum urea nitrogen (>40.05 mg/dL) or serum creatinine (>2.0 mg/dL) (Table IV).

DISCUSSION

This study demonstrates that simultaneously adding 2 RAS-blocking agents, a DRI (aliskiren) and an ARB (valsartan), to HCTZ was more efficacious than adding either of these agents alone in patients not adequately responding to HCTZ 25-mg monotherapy. HCTZ is a commonly used initial agent for the treatment of hypertension. After randomization, a group of patients remained on this HCTZ dose throughout the study to serve as control for the evaluation of the BP-lowering effects of other medication added to the HCTZ. The additional BP reduction and greater BP control rate observed with the triple combination compared with the 2-drug combinations confirmed that the use of 3 medications with different actions has more effect on lowering BP than the use of 2 agents.

The safety of the aliskiren/valsartan/HCTZ combination was comparable to HCTZ alone and the 2-drug combinations. These findings raise at least 2 important questions: (1) is the stepwise addition of antihypertensive medications the most effective approach in patients not responding to a single agent and (2) is the combination of a DRI and an ARB a useful regimen given that both agents act on the RAS system?

The stepwise approach calls for initiating antihypertensive therapy with a single agent and adding an additional drug if BP is not adequately controlled. This leads to the achievement of BP goal in a more timely manner[1,2] in many patients but may not be appropriate for patients with BP >20 mm Hg above systolic goal or 10 mm Hg above diastolic goal (>160/100 mm Hg). Sustained BP elevation potentially increases the risk of developing or worsening organ damage. Realizing these

drawbacks, JNC 7[1] and the European Society of Hypertension/European Society of Cardiology (ESH/ESC)[2] guidelines recommend the initiation of 2-drug treatment for patients whose BP is >160/100 mm Hg or for those with comorbidities, such as diabetes or coronary heart disease, and stage 1 hypertension (>140/90–160/100 mm Hg) who might benefit from more aggressive BP control. Applying the same rationale for the treatment of patients who do not adequately respond to a single-drug treatment, simultaneously adding 2 drugs might result in more efficient BP control for some patients compared with adding one drug at a time. In this study, the baseline DBP in select patients after 4 weeks of HCTZ treatment was >99 mm Hg (99.2–99.9 mm Hg, across groups); 52% of the patients had an SBP ≥160 mm Hg and/or DBP ≥100 mm Hg. It is likely that many of these patients would require at least 2 or possibly 2 additional drugs to achieve adequate BP control. The results indicated that 18% to 26% of additional patients achieved BP control (<140/90 mm Hg) with the triple-combination group when compared with patients who received 2 medications.

Aliskiren/HCTZ and valsartan/HCTZ combinations demonstrated significant BP reductions when compared with HCTZ alone. It should be noted that HCTZ dosage was not titrated to a higher dose. It is quite possible that some additional patients may have responded to a higher dosage. The aliskiren/valsartan/HCTZ combination produced even more BP reductions of 3 to 7/2 to 5 mm Hg than the double combinations, an additional benefit of the 3 drugs in a group of patients with uncontrolled hypertension. Our study excluded patients with severe hypertension and those with cardiovascular and other life-threatening events. The Framingham Heart Study[9] indicated that a 2-mm Hg reduction in average DBP could result in a 14% decrease in the risk of stroke and transient ischemic attacks and a 6% reduction in the risk of coronary artery disease. These data suggest that more aggressive BP-lowering might be beneficial. Although the study excluded patients with severe hypertension, the use of 3-drug therapy might be a feasible option in patients with markedly high BP or comorbidities.

There is no doubt that efficacy is not the only consideration for aggressive treatment of hypertension with multiple drugs. The safety and tolerability of these must also be carefully evaluated and compared with the component agents. In this study, the tolerability profile of the 3-drug combination was similar to other therapies, with no meaningful differences. Excessive BP reduction and its consequences (eg, hypotension, syncope) have been a concern when using aggressive antihypertensive regimens. In this study, the occurrence of hypotension and syncope was low (2 patients or 1.2% for each event) in the 3-drug combination group and not higher than those in the 2-drug group (1.3% for each event). Hyperkalemia, a potential safety concern for dual RAS blockade, occurred in 1 patient (0.6%) in the aliskiren/valsartan/HCTZ group; the patient's serum potassium level returned to normal without discontinuation of the study drugs. In this trial, for the aliskiren/valsartan/HCTZ combination, aliskiren was able to neutralize the reactive rise in PRA noted in the valsartan/HCTZ combination.

HCTZ activates RAS and causes an increase in renin concentration and activity. Thus, the use of an RAS inhibitor with a diuretic is a logical approach. In a study using the combination of an ARB and a renin inhibitor, Oparil and colleagues[10] reported that treatment with an aliskiren/valsartan combination was superior to component monotherapies in BP reduction and in achieving BP control. Our results further confirm that in patients not adequately responsive to HCTZ treatment, the combination of an RAS inhibitor and an ARB produced a greater BP-lowering effect as add-on therapy to HCTZ compared with each of the component therapies.

Combining 2 agents blocking the RAS in the treatment of hypertension and for organ protection has drawn increasing interest. Several studies have, however, yielded different results. Data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[11] in patients with vascular disease or high-risk diabetes have shown that despite the greater BP-lowering effect (2- to 3-mm Hg SBP reduction), the combination of an ARB (telmisartan) and an ACEI (ramipril) did not produce additional clinical benefit in comparison to the component monotherapies. However, Parving and colleagues[12] demonstrated that in hypertensive patients with type 2 diabetes mellitus and nephropathy, adding a DRI (aliskiren) to background therapy of an ARB (losartan) produced greater reduction in proteinuria than losartan alone despite similar BP reduction for the 2-treatment groups. As the degree of proteinuria is closely associated with the rates of renal and cardiovascular events, these data suggest a potential clinical benefit of an aliskiren and ARB combination. The somewhat different results in these studies

may be due to the classes of agents used. The combination of a DRI and an ARB might have a different organ-protective effect from the ARB and an ACEI combination. This needs to be further investigated.

CONCLUSIONS

An aliskiren/valsartan/HCTZ combination provides greater BP-lowering effect compared with the component double combinations with a similar tolerability profile in patients not adequately responding to low-dose HCTZ alone. The additive effect of a dual RAS blockade with aliskiren and valsartan has been demonstrated in patients with activated RAS caused by HCTZ treatment.

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