

Adv Ther (2011) 28(5):427–438.
DOI 10.1007/s12325-011-0014-4

ORIGINAL RESEARCH

Efficacy, Safety, and Tolerability of Valsartan/ Hydrochlorothiazide in Asian Patients with Essential Hypertension

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Received: November 2, 2010 / Published online: April 8, 2011
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ABSTRACT

Introduction: Previous studies have demonstrated that hypertensive patients need concomitant therapy with one or more drugs from different classes of antihypertensive agents to achieve their blood pressure control targets. We performed the first multinational observational study of valsartan/hydrochlorothiazide (HCTZ) single pill combination in Asia to determine the efficacy, safety, and tolerability in hypertensive patients. The objective of this multinational, multicenter, 24-week follow-up observational study is to evaluate the efficacy, safety, and

tolerability of valsartan/hydrochlorothiazide single pill combination in the treatment of essential hypertension in the Asia-Pacific region. **Methods:** A total of 7567 Asian patients who were diagnosed with stage 1 or stage 2 essential hypertension and who took at least one dose of valsartan/hydrochlorothiazide single pill combination were included in the statistical analyses. A total of 59% were taking antihypertensive medication at the time of the study. Eligible patients received valsartan/hydrochlorothiazide single pill combination 80/12.5 mg tablets orally once daily at visit 1. The investigator could decide the subsequent dose of valsartan/hydrochlorothiazide single pill combination for their patients, and efficacy, safety, and tolerability data were collected at week 4, 12, and 24. **Results:** Basal blood pressure was 155.9 ± 13.3 mmHg (systolic) and 96.3 ± 10.1 mmHg (diastolic). Response rates and control rates increased continuously from baseline to the study endpoint at week 24, when they reached 94.6% and 73.2%, respectively. Systolic and diastolic blood pressure reductions were -25.4 ± 15.2 mmHg and -14.9 ± 13.5 mmHg, respectively ($P < 0.001$). Using a four-point global assessment scale, 96.8% of the patients and physicians reported good, very good, or

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excellent for both their subjective efficacy and tolerability assessments. **Conclusion:** In this multicenter, multicountry study including 7567 Asian patients with hypertension, valsartan/hydrochlorothiazide single pill combination was found efficacious, well tolerated, and devoid of any serious adverse effects.

Keywords: Asian; combination therapy; efficacy; hypertension; tolerability; valsartan/hydrochlorothiazide single pill

INTRODUCTION

Hypertension is the most common cardiovascular condition in the world and is the leading preventable cause of morbidity and mortality due to coronary heart disease, stroke, heart failure, and kidney failure.¹ In the urban adult populations of Asia, the prevalence, using the criterion of blood pressure (BP) $\geq 140/90$ mmHg, varies between 15% and 35%, although it is lower in rural areas.²⁻⁴ Despite the availability of a wide range of antihypertensive drugs, mild to moderate hypertension still remains poorly controlled.⁵ Inadequate lowering of BP with antihypertensive therapy can be attributed to several factors, such as multiple pathophysiological mechanisms involved and the heterogeneity among patients, the failure of physicians to titrate or modify first-line therapy to reach the recommended target BP, and the lack of patient compliance.⁶

Despite the efficacy of monotherapy with a number of antihypertensive agents, approximately 70% of hypertensive patients require one or more antihypertensive drugs with different mechanisms of action in order to reach treatment targets.⁷ Therefore, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the World Health Organization (WHO) have

recently recommended combination therapy as a first-line approach for stage 2 hypertension.⁸ Combination therapy also has the advantage of achieving improved antihypertensive efficacy at low individual drug doses compared with those used in monotherapy and, therefore, has a lower incidence of adverse effects.⁸

Valsartan, an angiotensin II receptor blocker (ARB), lowers BP mainly by blocking the effects of angiotensin II on vascular smooth muscle.⁹ It also blocks the aldosterone-mediated retention of sodium and excretion of potassium in the distal tubule by preventing angiotensin-initiated aldosterone release from the adrenal gland.

Hydrochlorothiazide (HCTZ), a thiazide diuretic, is thought to lower BP primarily by decreasing sodium resorption in the renal distal convoluted tubules.^{10,11} This sodium depletion causes a reflex increase in plasma renin activity, a subsequent increase in angiotensin, and in aldosterone secretion, and urinary retention of sodium accompanied by excretion of potassium. Therefore, coadministration of an angiotensin II receptor antagonist like valsartan can lessen the potassium loss associated with the use of thiazide diuretics.¹²

Increasing amounts of evidence have confirmed that combination therapy is the preferred treatment regimen to achieve satisfactory control of BP in the majority of hypertensive patients.^{7,8} The combination of an ARB and low-dose HCTZ does not produce any major side effects and provides an antihypertensive action significantly greater than that of either drug given alone.¹²⁻¹⁶ The objective of this multinational observational study is to further evaluate the efficacy, safety, and tolerability of valsartan/HCTZ single pill combination (SPC) in the treatment of essential hypertension in a general clinical practice setting. The study design was selected with the

aim to collect data from real-world practice with a substantial cohort of Asian patients representative of the population being prescribed valsartan/HCTZ SPC in the Asia-Pacific region.

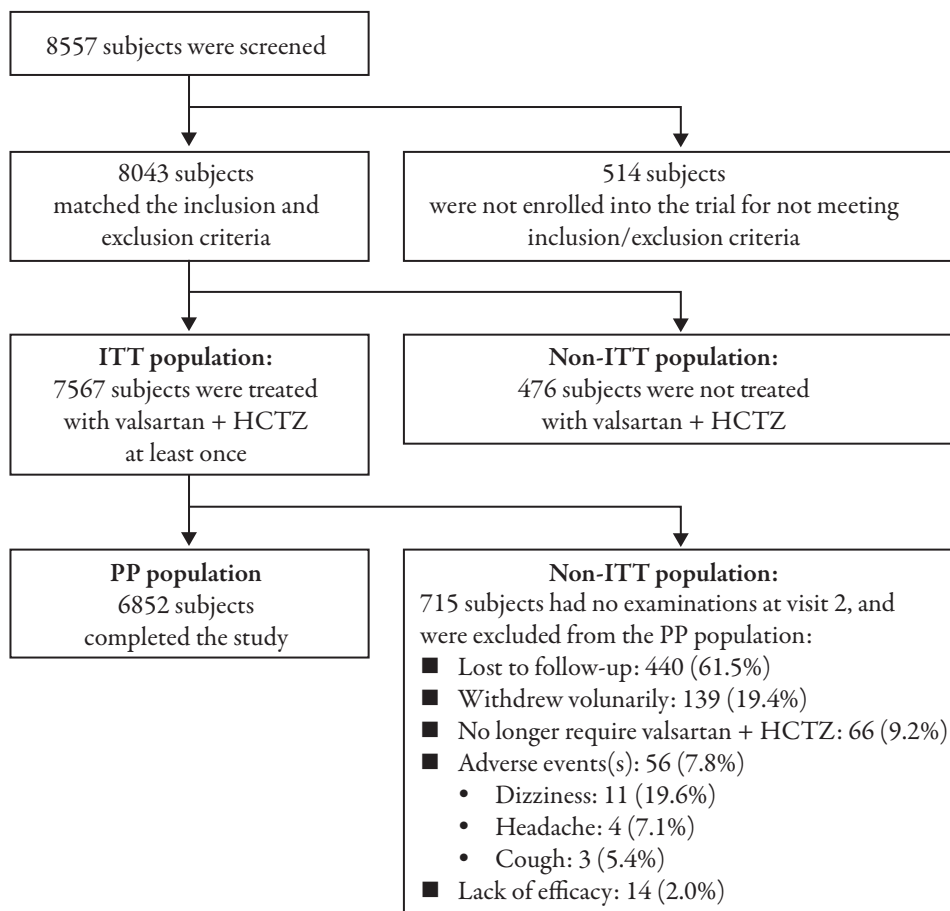
MATERIALS AND METHODS

Study Objectives

This multinational, open-label, observational, noncomparative, clinical decision-based titration study was conducted at 371 centers in Asia, including Bangladesh, India, Indonesia, Korea (South), Malaysia, Pakistan, Taiwan, and Thailand. A total of 8557 patients were enrolled in the study. Of these patients, 7567 took at least one dose of valsartan/HCTZ SPC and were

included in the statistical analysis, with 6852 completing the study (Figure 1). Inclusion criteria were (1) male or female subjects ≥ 18 and ≤ 65 years of age; (2) naïve patients with stage 1 (systolic blood pressure [SBP] 140-159 mmHg/diastolic blood pressure [DBP] 90-99 mmHg) or stage 2 (SBP ≥ 160 mmHg/DBP ≥ 100 mmHg) essential hypertension, or patients uncontrolled on current monotherapy or other combination therapy. Exclusion criteria were (1) women who were pregnant, intending to become pregnant or who were breastfeeding; (2) subjects with severe medical conditions that in view of the investigator prohibited participation in the study (eg, severe renal or hepatic impairment); and (3) hypersensitivity to valsartan/HCTZ SPC or any of the components in the formulation.

Figure 1. Study flow chart. ITT=intent to treat; PP=per protocol.



Baseline Antihypertensive Medications

Of the 13,936 records for baseline medications, 3450 were for antihypertensive therapy and 10,119 for nonantihypertensive therapy, and the medications named in the remaining 367(2.6%) records could not be reliably identified.

A total of 2106 (27.8%) were taking antihypertensive medication at the start of the study. About one-half (1193 patients, 56.6%) were on one, 609 patients (28.9%) on two, 221 patients (10.5%) on three, 56 patients (2.7%) on four, and 27 patients (1.3%) on more than four antihypertensive medications at baseline. Of these patients, 2,053 (97.5%) were taking antihypertensive medications that were not diuretics, and 210 (10.0%) of them were taking diuretics.

Of the 2053 patients who were taking antihypertensive medications that were not diuretics, 1409/2053 (68.6%) were taking a calcium channel blocker, 1114/2053 (54.2%) were taking beta blockers, 222/2053 (10.8%) were taking alpha blockers, 148/2053 (7.2%) were taking an angiotensin-converting enzyme inhibitor (ACEI), 72/2053 (3.5%) were taking an ARB, 11/2053 (<1%) were taking alpha 2 agonists, and 10/2053 (<1%) were taking direct vasodilators.

Of the 210 patients who were taking diuretics, 68/210 (32.4%) were taking high-ceiling diuretics, 44/210 (21.1%) were taking potassium-sparing diuretics, 34/210 (16.2%) were taking loop diuretics, 37/210 (17.6%) were taking thiazide-type diuretics, and 21/210 (10.0%) were taking low-ceiling diuretics.

Diagnosis of hypertension was based on JNC 7 guidelines¹⁷ stage 1 (SBP 140-159 mmHg/DBP 90-99 mmHg and stage 2 (SBP \geq 160 mmHg/DBP \geq 100 mmHg). As this was a noninterventional study, previous antihypertensive therapy could be continued according to the discretion of

the clinician. If the previous antihypertensive treatment duplicated the study drug treatment, the patients were switched from the original treatment in order to be enrolled in this study. The measurement of BP was performed according to usual clinical practice (Korotkoff sound for one-time sitting BP measurement or average BP of three-sitting BP measurement). The total duration of treatment with valsartan/HCTZ SPC was 24 weeks. All patients signed informed consent forms at the first visit.

The primary objective of the study was to evaluate the efficacy of valsartan/HCTZ SPC 80/12.5 mg, 160/12.5 mg, and 160/25 mg based on the percentage of responders. Responders were defined as those with SBP <140 mmHg and/or DBP <90 mmHg or a reduction of >10 mmHg in DBP and/or >20 mmHg in SBP compared to baseline values at week 24. The secondary objectives of the study were to evaluate the reduction in SBP and DBP, to assess the BP control rate (percentage of patients whose BP had reached the control values of SBP <140 mmHg and DBP <90 mmHg), to obtain subjective assessments by patients and physicians of the efficacy and tolerability of valsartan/HCTZ SPC at week 24, and to monitor safety throughout the study period.

Treatment

At visit 1 (week 0), eligible patients received a prescription for valsartan/HCTZ SPC 80/12.5 mg tablets orally once daily. At visit 2 (week 4), the investigator decided on the subsequent dose of valsartan/HCTZ SPC to be taken, based on the BP control achieved by the initial dose. If the BP was not controlled (defined as DBP \geq 90 mmHg and/or SBP \geq 140 mmHg), the dose of valsartan/HCTZ SPC was increased to 160/12.5 mg or 160/25 mg once daily, and this dose was continued until either the next visit or the end of the study; (2) if

the BP was controlled (DBP <90 mmHg and/or SBP <140 mmHg), the dose of valsartan/HCTZ SPC could also be modified to 160/12.5 mg or 160/25 mg if, in the investigator's clinical judgment, a further reduction in BP would be beneficial for the patient.

At all subsequent visits, visits 2 (week 4), visit 3 (week 12) and visit 4 (week 24), the investigator could modify the dose of valsartan/HCTZ SPC, based on the BP control achieved and the tolerability of the dosage used. If at any visit the patient's BP was not controlled with the maximum dose of valsartan/HCTZ SPC, the investigator had the option of adding another suitable antihypertensive, based on clinical judgment and experience. All concomitant therapy was allowed at the discretion of the investigators.

Outcome Measurement

Clinical outcome was measured in terms of the reduction in SBP and DBP. Mean±SD reductions in SBP and DBP were calculated from baseline (week 0) to the end of treatment (week 24). The BP control rate was defined as percentage of patients achieving the designated control BP (SBP <140 mmHg and DBP <90 mmHg). This rate was calculated using the frequency distribution at the end of treatment (week 24). Global assessment of efficacy and tolerability were both evaluated by physicians and patients using a four-point scale (excellent, very good, good, and poor). Frequency distribution was used to perform the analysis of these parameters at week 24. An adverse event was defined as any untoward medical occurrence or clinical investigation in a patient administered a pharmaceutical product and did not necessarily have a causal relationship to the treatment. Worsening of signs and symptoms present at the initial visit and the appearance of new signs and symptoms after valsartan/

HCTZ SPC administration were considered as adverse events. We did not examine potassium or creatinine levels or investigate coughs specifically, nor did we determine the percentage of diabetic patients in this cohort.

Statistical Analysis

Categorical variables were presented as counts and percentages, and the chi-square test was used to test the associations between categorical variables; continuous variables were presented as mean±SD. SBP and SBP reductions between females and males were compared by independent two-sample *t* test. Repeated analysis of covariance was performed to detect differences in BP between the initial and the four treatment time points. A paired *t* test was performed to detect the difference in BP between two time points. Cohen's kappa was performed to demonstrate agreement of the global assessments for efficacy and tolerability between the patient and their physician (Cohen's kappa: 0-0.2, slight agreement; 0.2-0.4, fair agreement; 0.4-0.6, moderate agreement; 0.6-0.8, substantial agreement; 0.8-1.0, almost perfect agreement) with a significance level set at 0.05. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline Characteristics

All 7567 patients who took at least one dose of valsartan/HCTZ SPC were included in the statistical analysis. Patient demographics and baseline characteristics are shown in Table 1. In all, 55% of patients had stage 2 and 45% stage 1 hypertension. The mean BP values at baseline were 155.9±13.3 mmHg (SBP) and 96.3±10.1 mmHg (DBP). All patients were Asian, with the

Table 1. Patient demographics and baseline characteristics.

Characteristic	Total (<i>n</i> =7567)
Sex, <i>n</i> (%):	
Female	3147 (41.6)
Male	4420 (58.4)
Age, years (mean±SD)	52.8±8.3
Height, cm (mean±SD)	163.0±12.4
Weight, kg (mean±SD)	69.4±12.6
SBP, mmHg (mean±SD)	155.9±13.3
DBP, mmHg (mean±SD)	96.3±10.1
HR, beats per minute (mean±SD)	76.2±11.8
Country, <i>n</i> (%):	
Korea	3420 (45.2)
Taiwan	2493 (32.9)
Pakistan	741 (9.8)
Bangladesh	392 (5.2)
India	240 (3.2)
Indonesia	235 (3.1)
Malaysia	46 (0.6)

DBP=diastolic blood pressure; HR=heart rate;
SBP=systolic blood pressure.

following country distribution: Korea (45.2%), Taiwan (32.9%), Pakistan (9.8%), Bangladesh (5.2%), India (3.2%), Indonesia (3.1%), and Malaysia (0.6%).

Efficacy and Tolerability of Valsartan/HCTZ SPC

The dose of valsartan/HCTZ SPC in the 0-4 week period was 80/12.5 mg for all patients. In the 4-12 week period, 82.3% of patients were continued on this dosage, 14.4% were titrated to a 160/12.5 mg dosage, and 2.6% to a 160/25 mg dosage. In the 12-24 week period, the percentage of patients taking the low, initial dosage form remained unchanged (82.3%), the percentage taking the medium dosage form increased slightly (to 16%) and the percentage taking the highest dosage decreased slightly (from 2.6% to 1.8%). SBP and DBP decreased continuously and significantly

throughout the study period (Figure 2) (all *P* values <0.05), and were 155.9±13.3 mmHg and 96.3±10.1 mmHg, respectively (at baseline, 140.7±13.3 mmHg and 87.2±9.5 mmHg at week 4, 134.7±12.1 mmHg and 83.8±13.1 mmHg at week 12, and 130.5±11.4 mmHg and 81.5±11.8 mmHg at week 24).

Response rates, BP control rates, and BP reductions are summarized in Table 2. Response rate and control rate increased continuously from baseline to the end of the study, week 24, when they reached 94.6% and 73.2%, respectively. Mean SBP and DBP reductions were -25.4±15.2 mmHg and -14.9±13.5 mmHg, respectively at the end of the study (week 24, *P*<0.001). Significant reductions compared to baseline values in both SBP and DBP were also seen at weeks 4 and 12 (*P*<0.001).

The global subjective efficacy assessment for valsartan/HCTZ SPC is summarized in Table 3.1. Almost all patients and physicians (96.8%) reported good, very good, or excellent for efficacy, and 80.6% of the patients reported the same global efficacy assessment as their physicians.

Figure 2. Serial changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mean±SD) from baseline to week 24. *Indicates a significant difference in blood pressure compared to baseline (*P* values <0.05). †Indicates a significant difference in blood pressure compared to week 4 visit (*P* values <0.05). ‡Indicates a significant difference in blood pressure compared to week 12 visit (*P* values <0.05).

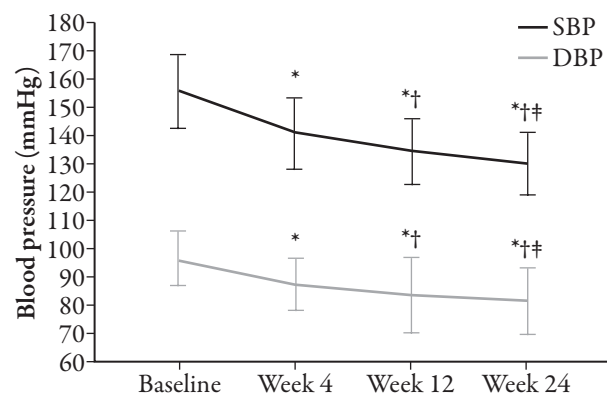


Table 2. Efficacy endpoints at weeks 4, 12, and 24.

Endpoint	Week 4 (n=7298)	Week 12 (n=6832)	Week 24 (n=6573)
DBP reduction >10 mmHg, n (%)	2162 (29.6)	3541 (51.8)	4254 (64.7)
SBP reduction >20 mmHg, n (%)	1686 (23.1)	2899 (42.4)	3774 (57.4)
SBP reduction >20 mmHg or DBP reduction >10 mmHg, n (%)	2804 (38.4)	4413 (64.6)	5105 (77.7)
DBP <90 mmHg, n (%)	3830 (52.5)	5064 (74.1)	5527 (84.1)
SBP <140 mmHg, n (%)	2747 (37.6)	4335 (63.5)	5243 (79.8)
SBP <140 mmHg or DBP <90 mmHg, n (%)	4366 (59.8)	5553 (81.3)	5956 (90.6)
Responder, n (%)*	4919 (67.4)	6022 (88.1)	6216 (94.6)
Blood pressure controlled, n (%)†	2211 (30.3)	3846 (56.3)	4814 (73.2)
Reduction of blood pressure, mean±SD:			
Systolic	-15.27±14.10	-21.17±14.90	-25.38±15.23
Diastolic	-9.12±9.79	-12.54±14.17	-14.85±13.51

Missing values among the intent-to-treat (ITT) population were 269 (3.6%), 735 (9.7%), and 994 (13.1%) at week 4, week 12, and week 24, due to no blood pressure examinations.

*Responders were defined as those patients with SBP <140 mmHg and/or DBP <90 mmHg, or a reduction of >10 mmHg in DBP and/or a reduction of >20 mmHg in SBP compared to baseline.

†Blood pressure controlled was defined as SBP <140 mmHg and DBP <90 mmHg.

DBP=diastolic blood pressure; SBP=systolic blood pressure.

A significant Cohen’s kappa of 0.755 ($P<0.001$) showed moderate agreement for efficacy assessments between patients and physicians.

The global assessment for tolerability of valsartan/HCTZ SPC is summarized in Table 3.2. Again, almost all patients and physicians (96.8%) reported good, very good, or excellent for the tolerability assessment, and 81.1% of the patients reported the same global assessments as their physicians. A significant Cohen’s kappa

of 0.768 ($P<0.001$) showed moderate agreement for tolerability assessments between patients and physicians.

Association Between Treatment Response and Age

A significant association between age and response was found at week 4; the response rates were 65.6% for those younger than 50 years and

Table 3.1. Agreement of global assessment for efficacy by patients and physicians (n=6705).

Assessment for efficacy		By patients (n=6705)				Total
		Poor	Good	Very good	Excellent	
By physicians, n (%)	Poor	110 (1.6)	11 (0.2)	1 (0.0)	0 (0.0)	122 (1.8)
	Good	73 (1.1)	1196 (17.8)	225 (3.4)	9 (0.1)	1503 (22.4)
	Very good	17 (0.3)	370 (5.5)	2,711 (40.4)	219 (3.3)	3317 (49.5)
	Excellent	5 (0.1)	24 (0.4)	345 (5.1)	1389 (20.7)	1763 (26.3)
Total, n (%)		205 (3.1)	1601 (23.9)	3282 (48.9)	1617 (24.1)	6705 (100.0)

n=6705, instead of 7567, due to 862 (11.4%) subjects in the intent-to-treat population who had no assessment for efficacy either by themselves or by physicians.

Table 3.2. Agreement of global assessment for tolerability by patients and physicians ($n=6671$).

Assessment for tolerability		By patients ($n=6671$)				Total
		Poor	Good	Very good	Excellent	
By physicians, n (%)	Poor	112 (1.7)	14 (0.2)	2 (0.0)	0 (0.0)	128 (1.9)
	Good	68 (1.0)	1245 (18.7)	223 (3.3)	10 (0.1)	1546 (23.2)
	Very good	14 (0.2)	341 (5.1)	2,647 (39.7)	184 (2.8)	3186 (47.8)
	Excellent	4 (0.1)	35 (0.5)	341 (5.1)	1431 (21.5)	1811 (27.1)
Total, n (%)		198 (3.0)	1635 (24.5)	3213 (48.2)	1625 (24.4)	6671 (100.0)

$n=6671$ instead of 7567 because 896 (11.8%) subjects in the intent-to-treat population had no assessment for tolerability either by themselves or by physicians.

68.5% for others older than 50 years ($P=0.010$). At week 12 and week 24, no significant association with age was found for response rate and BP control rate. For those patients younger than 50 years, DBP was reduced about 1 mmHg more than in patients older than 50 years of age at all times measured ($P<0.001$) (Supplementary Table 1).

Association Between Treatment Response and Gender

At week 4, the response rate and control rate in females was significantly higher than in males (response rate: 69.6% vs. 65.8%, $P=0.001$; control rate: 32.9% vs. 28.4%, $P<0.001$), and SBP reduction in females was significantly greater than that in males (-15.96 ± 14.73 vs. -14.79 ± 13.62 mmHg, $P=0.001$). At weeks 12 and 24, DBP reduction in females was significantly less than that in males (-11.89 ± 18.25 vs. -12.99 ± 10.37 mmHg at week 12, $P=0.002$; -14.45 ± 10.21 vs. -15.13 ± 15.40 mmHg at week 24, $P=0.046$) (Table 4).

Safety of Valsartan/HCTZ SPC

The safety of valsartan/HCTZ SPC was assessed by the number of adverse events that occurred during the study period. A total of 1747

adverse events were recorded for patients who took valsartan/HCTZ SPC at least once, and of these events, 1582 (90.6%) were thought to be unrelated to the study drug. Among the 7567 patients, 1082 patients (14.3%) experienced at least one adverse event, 262 patients (3.46%) reported two adverse events, and 152 patients (2.01%) reported more than two adverse events. Four (0.23%) serious adverse events were reported, including coronary artery disease, hypoglycemia, non-ST elevation myocardial infarction, and upper gastrointestinal bleeding. None of these serious adverse events were suspected to be due to valsartan/HCTZ SPC administration.

DISCUSSION

In this multinational observational study, significant SBP and DBP reduction was found at all time points during the study, with early achievement of the BP goal (140.7/87.2 mmHg, at week 4) and additional significant reduction at weeks 12 and 24. By the end of the study (week 24), almost all (94.6%) patients were responsive to valsartan/HCTZ SPC, and 73.2% of these responsive patients achieved the desired degree of BP control. Based on the proportion of patients achieving the desired SBP and DBP values, valsartan/HCTZ SPC exhibited a high

Supplementary Table 1. Association between age and efficacy endpoints.

	Week 4 (n=7298)		Week 12 (n=6832)		Week 24 (n=6573)				
	Age <50 years (n=2723)	Age ≥50 years (n=4575)	P value	Age <50 years (n=2542)	Age ≥50 years (n=4445)	P value	Age <50 years (n=4290)	Age ≥50 years (n=4128)	P value
Responder, n (%)†	1785 (65.6)	3134 (68.5)	0.010*	2225 (87.5)	3797 (88.5)	0.230	2310 (94.5)	3906 (94.6)	0.822
BP controlled, n (%)‡	842 (30.9)	1369 (29.9)	0.369	1459 (57.4)	2387 (55.6)	0.158	1777 (72.7)	3037 (73.6)	0.430
SBP reduction, mean±SD	-15.39±14.02	-15.20±14.16	0.588	-21.22±15.05	-21.14±14.82	0.827	-25.27±14.84	-25.44±15.46	0.659
DBP reduction, mean±SD	-9.84±9.61	-8.70±9.87	<0.001*	-13.46±9.85	-11.99±16.16	<0.001*	-15.60±9.81	-14.41±15.27	<0.001*

*P<0.05 indicated that there was significant association between age groups and the corresponding variable.

†Responders were defined as those patients with SBP <140 mmHg and/or DBP <90 mmHg, or a reduction of >10 mmHg in DBP and/or a reduction of >20 mmHg in SBP compared to baseline.

‡BP controlled was defined as SBP <140 mmHg and DBP <90 mmHg.

BP=blood pressure; diastolic blood pressure=DBP; systolic blood pressure=SBP.

Table 4. Association between gender and efficacy endpoints.

	Week 4 (n=7298)		Week 12 (n=6832)		Week 24 (n=6573)				
	Female (n=3026)	Male (n=4272)	P value	Female (n=2814)	Male (n=4018)	P value	Female (n=2699)	Male (n=3874)	P value
Responder, n (%)†	2107 (69.6)	2812 (65.8)	0.001*	2467 (87.7)	3555 (88.5)	0.323	2551 (94.5)	3665 (94.6)	0.912
BP controlled, n (%)‡	997 (32.9)	1214 (28.4)	<0.001*	1608 (57.1)	2238 (55.7)	0.244	1980 (73.4)	2834 (73.2)	0.865
SBP reduction, mean±SD	-15.96±14.73	-14.79±13.62	0.001*	-21.35±14.89	-21.04±14.91	0.391	-25.60±15.44	-25.22±15.08	0.330
DBP reduction, mean±SD	-8.88±9.99	-9.30±9.65	0.073	-11.89±18.25	-12.99±10.37	0.002*	-14.45±10.21	-15.13±15.40	0.046*

*P<0.05 indicated that there was significant association between age groups and the corresponding variable.

†Responders were defined as those patients with SBP <140 mmHg and/or DBP <90 mmHg, or a reduction of >10 mmHg in DBP and/or a reduction of >20 mmHg in SBP compared to baseline.

‡BP controlled was defined as SBP <140 mmHg and DBP <90 mmHg.

BP=blood pressure; diastolic blood pressure; SBP=systolic blood pressure.

degree of efficacy in this population (that is, in Asian adults, male and female naïve patients with stage 1 or stage 2 hypertension, or who were poorly controlled on their respective ongoing monotherapy or combination therapy).

Results of population studies vary by countries, as well as different prescription behaviors. Low prescription rates for combination therapy, 42.2% and 35.3%, were reported in studies from India and Japan, respectively, and ARB/HCTZ was not the most popular combination selected.^{18,19} In contrast, more than half (64%) of US hypertensive patients were prescribed combination therapy, with the majority of these prescriptions (27%) as ARB or ACEI in combination with diuretics.²⁰

A previous descriptive cross-sectional study reported that only 59% of hypertensive patients were under adequate control with treatment.²¹ A meta-analysis of several randomized, double-blind studies comparing valsartan monotherapy with combination treatment²² concluded that combination therapy was more effective in terms of response rate.

In the current study, we noticed that the younger patients (<50 years old) showed more DBP reduction than older patients. However, a current study by Asmar and Oparil showed older patients (>65 years old) achieve a greater DBP reduction than younger patients.²³ Although the difference was only 1 mmHg, it was statistically significant. The correlation between age and BP reduction will require additional confirmation in future investigations, and the clinical interpretation should be further discussed.

Regardless, in the current study, females showed a significantly smaller DBP reduction than males at week 12 and week 24. However, the difference between males and females was only 1 mmHg, and the significance is marginal at week 24. In the Asmar and Oparil study, females also showed a 1 mmHg smaller DBP

reduction than males, but this difference was not statistically significant.²³

Treatment with valsartan/HCTZ SPC was well tolerated for most patients, and almost all patients rated the tolerability with good or better. Almost all patients also rated the combination as efficacious, but because mild hypertension is symptomless, this subjective judgment reflected whether the patient's BP had reached a value the patient thought acceptable, rather than whether actual control had been achieved.

Choice of antihypertensive drugs depends on cost, anticipated side effects, and the physician's familiarity with the drug. Clinical trials have shown valsartan/HCTZ to be more effective than either drug alone and to have an adverse effect profile similar to that of placebo.¹⁹ The current study is the largest study to date, and includes 7567 Asian patients in a general clinical practice setting treated with valsartan/HCTZ SPC. The results reflect a real life situation as the patients included in this study represent the general population being prescribed valsartan/HCTZ SPC specifically in the Asia-Pacific region. The low incidence of adverse effects confirmed the safety of treatment in this study cohort. The results also confirm that combination therapy as first-line approach in stage 2 hypertension as recommended by WHO and the JNC⁸ is efficacious and well tolerated in Asian patients. However, 45% of the patients in the study had stage 1 hypertension, and because we did not investigate thiazide monotherapy, we cannot say whether valsartan/HCTZ is more efficacious than thiazide monotherapy in stage 1 hypertension. But in cases where two drugs need to be prescribed, it has been demonstrated that SPC treatment is associated with better compliance and a smaller pill burden. Antihypertensive therapy is always long lasting. Further research is required with this drug combination in Asian hypertension patients beyond 24 weeks of treatment in order

to confirm that the benevolent safety profile and efficacy can be maintained in the long run. Whether first line combination therapy has an effect on the number of therapies required in the future in order to obtain BP control will also be in the area of interest.

One limitation of the study was that there was a lack of data on patients who changed their nonstudy antihypertensive drug(s) during the course of the study. Another is that there was insufficient data necessary to perform subgroup analyses.

CONCLUSION

In summary, this multicenter, multicountry study consisting of 7567 Asian patients with essential hypertension, demonstrated valsartan/HCTZ SPC to be highly effective, well tolerated, and devoid of any serious adverse effects in a general practice setting.

ACKNOWLEDGMENTS

We thank the study participants and their families for their personal time and commitment to this project. The current study was sponsored by Novartis, Inc. for postmarketing surveillance of valsartan/HCTZ SPC with regards of its efficacy, tolerability, and safety profiles in Asia-Pacific patients. JW and ND are employees of Novartis and are therefore eligible for Novartis stock and stock options. W-TL and J-EP have received research grants and investigator fees from Novartis. The authors have no conflicts of interest to declare.

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