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Efficacy and safety of valsartan in hypertensive Taiwanese patients: Post-marketing surveillance study

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Abstract

Objective. To evaluate the efficacy and safety of valsartan in Taiwanese patients with essential hypertension. *Methods.* This 12-week multi-center, open-label, observational, post-marketing surveillance study enrolled 2046 hypertensive patients who were prescribed valsartan 80 or 160 mg as monotherapy or in combination with other antihypertensives based on clinical judgment. The primary endpoint was the incidence rate of dizziness with valsartan 160 mg monotherapy or combination therapy at Week 4. Secondary endpoints included the blood-pressure-lowering efficacy and the overall safety and tolerability of valsartan at Weeks 4 and 12. *Results.* The monotherapy and combination groups had comparable baseline characteristics. At Week 4, monotherapy was found non-inferior to combination for incidence rate of dizziness (monotherapy, 9.25%; combination, 10%; difference in incidence of dizziness, 0.75%; 95% CI − 0.61% to 2.12%; non-inferiority margin, −1.33%; Wald Test approach). Greater blood pressure (BP) reduction was noted at Week 12 than at Week 4. The antihypertensive effect was greater with combination therapy and the 160-mg dose. BP control (systolic <140 mmHg or diastolic <90 mmHg) was achieved in 80–90% patients. Valsartan was well tolerated; most commonly reported adverse events included dizziness, headache, constipation and cough. *Conclusion.* Valsartan is an effective treatment option for essential hypertension in Taiwanese patients.

Key Words: *Blood pressure, dizziness, post-marketing surveillance, safety, Taiwan, valsartan*

Introduction

Valsartan is an orally active, non-peptide angiotensin receptor blocker (ARB) extensively used for the treatment of hypertension and heart failure worldwide for over a decade (1,2). The drug has been approved for the initial treatment of essential hypertension in Taiwan (2007) and USA (2), and has also been included as a first-line therapeutic option in hypertensive patients by the European Society of Hypertension/European Society of Cardiology (ESH/ESC) (3). Its antihypertensive action occurs because of the site specificity of valsartan, causing inhibition of the vasoconstrictor and pressor response exerted by angiotensin II; the subsequent decrease in sodium retention and aldosterone secretion is suggested to be responsible for reduction of the adverse reactions normally associated with angiotensin-converting enzyme (ACE) inhibitors (4). Valsartan is used either

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as monotherapy or in combination with other antihypertensive agents in doses of 80, 160 and 320 mg (1).

The efficacy of valsartan is known to be independent of age, sex and race, and is equivalent to that of other antihypertensive drugs like calcium antagonists, ACE inhibitors and thiazide diuretics (5). Various studies have compared valsartan with placebo (6) and other blood-pressure-lowering agents such as enalapril (7,8), amlodipine (9,10), losartan (11), ACE inhibitors (12) and beta-blockers (13). The results of these studies indicate that valsartan is safe, effective and well tolerated in patients with mild to moderate hypertension.

Valsartan has a good overall safety profile, with very low incidence of side-effects, almost similar to that of placebo (1,3). Headache, dizziness and fatigue are frequently observed in valsartan recipients; however, dizziness is the most common reason for discontinuation of therapy (4). Dizziness is also commonly observed in the general population, with an incidence rate of 3.1% and a prevalence rate of about 23% (14). The incidence of dizziness with valsartan 20–160 mg is shown to be 2–3.5%, which is much lower than 5.4% reported with placebo; increase in dosage also leads to increased incidence of dizziness (6). This side-effect has been attributed to the first-dose hypotensive effect; therefore, it is suggested that ARBs should be initially started in low doses and then titrated according to their hypertensive effect (15). Our study assessed the incidence of dizziness associated with the higher dose of valsartan in monotherapy and in combination with other antihypertensive drugs in Taiwanese patients. We considered dizziness from a dual perspective, i.e. efficacy and safety. Although the safety and tolerability profile of valsartan is well documented in the Caucasian, African-American and Middle Eastern populations (4,16,17), it may vary in the Asian population because of differences in body size.

The objective of this study is to evaluate the incidence rate of dizziness and the efficacy and safety of valsartan (80 and 160 mg) in monotherapy and in combination with other antihypertensive drugs (combination therapy) in the Taiwanese population.

Methods

Study design

This was a 12-week, multi-center, open-label, non-comparative, observational, post-marketing surveillance study, designed and implemented in accordance with ICH GCP guidelines and approval from the local ethics committee (Ethics Review Board). The primary objective was to evaluate the incidence rate of dizziness after 4 weeks of treatment with valsartan 160 mg as monotherapy or combination therapy. The secondary objectives included: (i) evaluation of safety and tolerability of valsartan 80 or 160 mg monotherapy or combination therapy at Week 4 and Week 12; (ii) evaluation of the blood-pressure-lowering effect of these treatments at Week 4 and Week 12; and (iii) observation of current treatment trends of hypertension, including percentage of various regimens at Week 0 and changes at Week 4 and Week 12.

Patients

Individuals aged ≥18 years and diagnosed with hypertension (sitting systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg) were included in the study. Individuals with known hypersensitivity to valsartan or any component in the formulation; pregnant or breastfeeding women; and individuals with severe medical conditions, using any other investigational drugs at the time of enrolment, or with a history of any malignancy within the previous 5 years (except localized basal cell carcinoma of the skin) were excluded from the study. The protocol was in accordance with the ethical principles laid down in the Declaration of Helsinki, and all patients provided written informed consent.

Treatment and assessments

At the initial visit, in addition to physical examination, relevant medical history and information on concomitant medications (including antihypertensives) were recorded. Blood pressure (BP) was recorded in the sitting position in the upper arm. Based on the physician's clinical judgment, patients were prescribed valsartan 80 or 160 mg monotherapy or combination therapy. At the second visit (Week 4), BP was recorded, and any change in antihypertensive medication and adverse events (AEs) were noted. Treatment changes were determined by the physician based on BP control and tolerability. Similar assessments were made at the final visit (Week 12).

Outcome measures

The incidence rate of dizziness at Week 4 with valsartan 160 mg as monotherapy or combination therapy (primary endpoint) was assessed based on the patient's response to the standard question, "Did you feel or sense dizziness in the past 4 weeks?" The blood-pressure-lowering effect of valsartan was assessed based on the mean change from baseline in SBP and DBP at Week 4 and Week 12. An exploratory analysis was performed to compare the blood-pressure-lowering effect between the 80- and 160-mg doses. Furthermore, a subgroup analysis was conducted for patients with baseline SBP >160 and ≤160 mmHg and baseline DBP >100 and ≤100 mmHg. The BP control rate, defined as the proportion of

patients with SBP <140 mmHg or DBP <90 mmHg, with valsartan 80 and 160 mg as monotherapy and combination therapy at Week 4 and Week 12 was also determined. The treatment trend was assessed based on the percentage of patients prescribed valsartan 80 or 160 mg at baseline and the percentage of patients requiring combination therapy or a switch to another monotherapy or another combination therapy at Week 4 and Week 12. The safety and tolerability of valsartan 80 or 160 mg monotherapy or combination therapy was assessed based on the incidence of AEs, serious adverse events (SAEs), and their relationship to the study drug.

Statistical analysis

Since the incidence rate of dizziness with valsartan 160 mg is 4% in Caucasians, under the non-inferiority hypothesis and with 1.33% as the clinical margin, an estimated sample size of 1336 patients would be required to reach statistical significance for the eligible population (alpha = 0.05; 1 − beta = 0.8). If the actual incidence rate of dizziness was expected to be 4.2% (5% more than reference), at least 1937 patients would be required to be enrolled in this study. The primary efficacy evaluation was conducted on the intent-to-treat (ITT) population comprising all enrolled patients who received at least one dose of valsartan and completed at least the 4-week core period. Secondary endpoints and safety were evaluated in the safety population comprising all enrolled patients who received at least one dose of valsartan during the study period.

For the primary variable, a frequency table was generated using descriptive statistics, and the incidence rate of dizziness was compared between the monotherapy and combination groups by using Pearson chi-square or Fisher's exact test. For the secondary variables, all continuous variables were summarized with descriptive statistics, and categorical variables were tabulated as frequencies and percentages. For comparison of assessments, the overall change in SBP and DBP from baseline and change in SBP and DBP by visit were analyzed by analysis of variance (ANOVA) or covariance (ANCOVA). All analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA); $p < 0.05$ was considered statistically significant.

Results

A total of 2046 patients were enrolled in the study, with 867 in monotherapy and 1179 in the combination group (Figure 1). The monotherapy and combination groups were balanced in terms of demographics and baseline characteristics (Table I). Over the study period (three visits), 53–56% patients received valsartan 80 mg and 43–44% patients received the 160-mg dose. The mean (±SD) duration of drug exposure was 81.48 ± 16.87 days in patients receiving valsartan 80 mg and 80.19 ± 18.55 days in those receiving valsartan 160 mg.

Efficacy

At Week 4, dizziness was experienced by 27 (9.25%) and 52 (10.00%) patients receiving valsartan 160 mg in the monotherapy and combination therapy groups, respectively, in the ITT population. The difference in the incidence rate of dizziness between the monotherapy and combination therapy groups was 0.75% (95% CI − 0.61% to 2.12%). The lower margin of the confidence interval (−0.61%) was greater than the margin of the non-inferiority hypothesis (−1.33%). Thus, the monotherapy group was found to be non-inferior to the combination therapy group with respect to the incidence rate of dizziness with valsartan 160 mg at Week 4. Results of supplemental

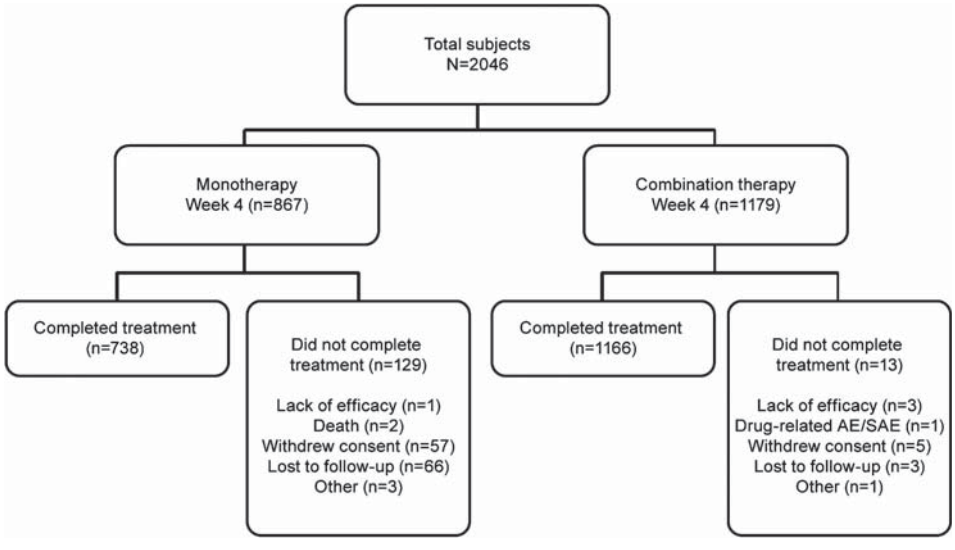

Figure 1. Patient disposition flow chart.

Table I. Baseline demographics and clinical characteristics of the study population.

Baseline characteristics	Monotherapy, $n = 867$	Combination therapy, $n = 1179$
Age (years), mean ± SD	61.58 ± 13.61	62.59 ± 13.31
Gender, *n* (%)		
Male	479 (55.25%)	647 (54.88%)
Female	388 (44.75%)	532 (45.12%)
Smoking history, *n* (%)		
Yes	157 (18.11%)	211 (17.91%)
No	710 (81.89%)	967 (82.09%)
Baseline sitting SBP (mmHg), mean ± SD	154.34 ± 13.03	154.41 ± 14.75
Baseline sitting DBP (mmHg) mean ± SD	89.19 ± 11.04	88.73 ± 11.04

analysis in the per-protocol population were in agreement with the above results (data not shown).

The decreases in SBP and DBP in the combination therapy group were greater than those in the monotherapy group at both Week 4 and Week 12 (Table IIa). The difference between the monotherapy and combination therapy groups was statistically significant only in the case of SBP reduction at Week 12 (−18.07 ± 13.64 mmHg vs −20.37 ± 17.49 mmHg; $p = 0.0293$). An exploratory analysis comparing the BP reduction between the 80- and 160-mg doses in monotherapy and combination therapy showed that the reductions in both SBP and DBP were greater with the 160-mg dose than with the 80-mg dose, although statistical significance was reached only for SBP reduction (Table IIb). Furthermore, the reduction in BP from baseline was greater at Week 12 than at Week 4 for both doses as well as for monotherapy and combination therapy. Subgroup analysis showed that the mean reduction in SBP and DBP in the >160/100 mmHg subgroup was almost double of that in the ≤160/100 mmHg subgroup in patients receiving valsartan 80 or 160 mg as monotherapy or combination therapy at both Week 4 and Week 12 (Figures 2a and 2b). High BP control rates of 80% and 90% were obtained at Week

Table IIa. Overall change in blood pressure by treatment groups.[a]

Change in blood pressure	Monotherapy	Combination therapy	*p*-value
Systolic blood pressure			
Baseline to Week 4	(*n* = 683)	(*n* = 1223)	
Mean ± SD, mmHg	–14.38 ± 14.26	–15.01 ± 16.25	0.6432
95% CI	(−15.45 to − 13.31)	(−15.93 to − 14.10)	
Baseline to Week 12	(*n* = 529)	(*n* = 1211)	
Mean ± SD, mmHg	–18.07 ± 13.64	–20.37 ± 17.49	0.0293*
95% CI	(−19.23 to − 16.90)	(−21.35 to − 19.38)	
Diastolic blood pressure			
Baseline to Week 4	(*n* = 683)	(*n* = 1223)	
Mean ± SD, mmHg	–6.97 ± 11.16	–7.62 ± 11.36	0.3108
95% CI	(−7.81 to − 6.13)	(−8.26 to − 6.98)	
Baseline to Week 12	(*n* = 529)	(*n* = 1211)	
Mean ± SD, mmHg	–9.42 ± 10.93	–10.34 ± 12.24	0.1193
95% CI	(−10.35 to − 8.48)	(−11.03 to − 9.65)	

[a]Safety population, by treatment groups; *$p < 0.05$ between treatment groups.

Table IIb. Overall change in blood pressure by dose.[a]

Change in blood pressure	80 mg valsartan	160 mg valsartan	*p*-value
Systolic blood pressure			
Baseline to Week 4	(*n* = 1013)	(*n* = 812)	
Mean ± SD mmHg	–13.24 ± 13.24	–16.53 ± 17.58	0.0001*
95% CI	(−14.06, − 12.43)	(−17.74, − 15.32)	
Baseline to Week 12	(*n* = 879)	(*n* = 729)	
Mean ± SD mmHg	–18.11 ± 13.08	–21.64 ± 18.94	0.0001*
95% CI	(−18.98, − 17.25)	(−23.02, − 20.27)	
Diastolic blood pressure			
Baseline to Week 4 (*n*)	(*n* = 1013)	(*n* = 812)	
Mean ± SD mmHg	–7.01 ± 9.83	–7.72 ± 12.72	0.1902
95% CI	(−7.61, − 6.40)	(−8.60, − 6.84)	
Baseline to Week 12 (*n*)	(*n* = 879)	(*n* = 729)	
Mean ± SD mmHg	–10.02 ± 10.44	–10.05 ± 13.13	0.9616
95% CI	(−10.71, − 9.33)	(−11.00, − 9.09)	

[a]Safety population, by dose; *$p < 0.001$ between doses.

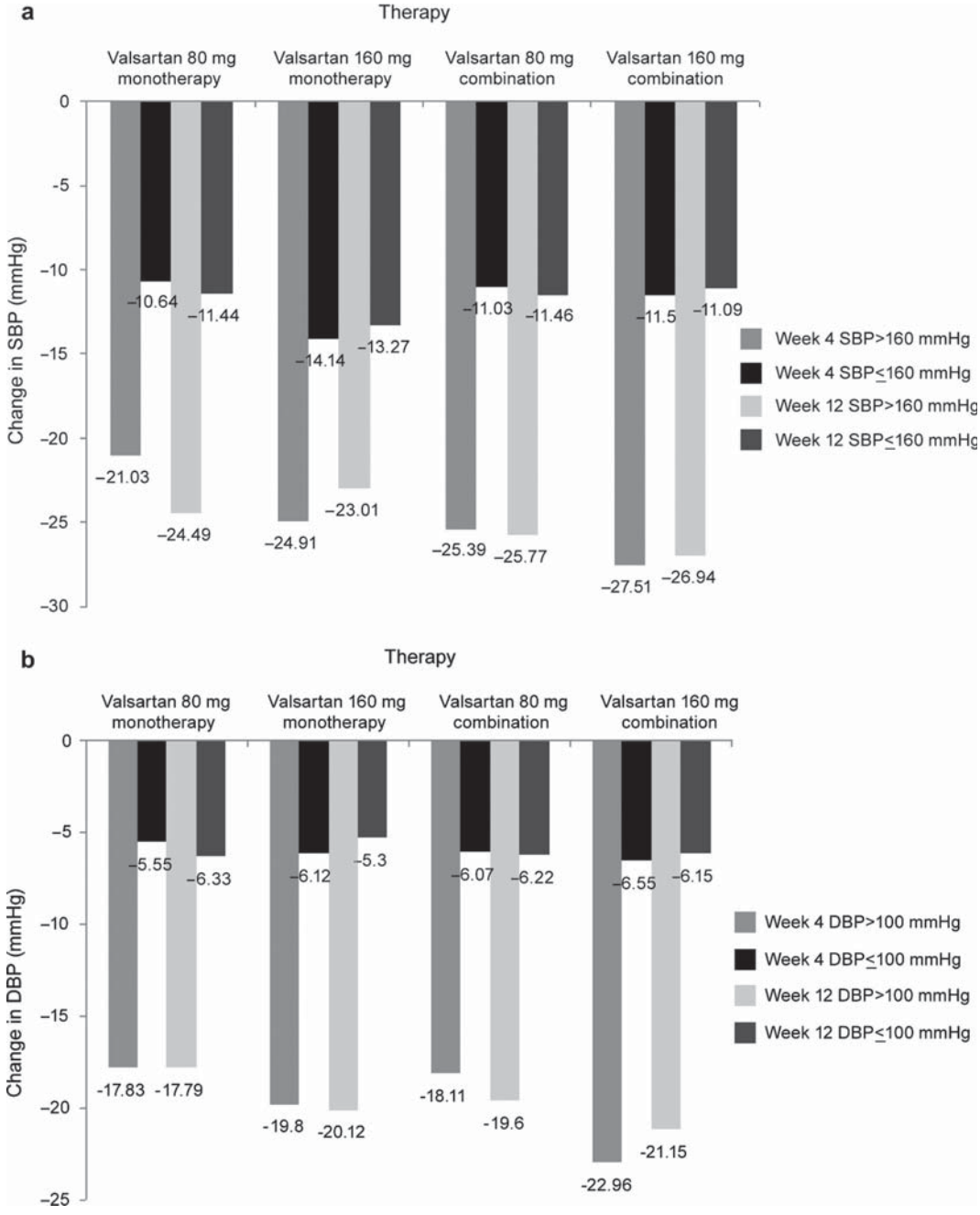

Figure 2. (a) Mean change in systolic blood pressure (SBP) at Week 4 and Week 12 (subgroup analysis). (b) Mean change in diastolic blood pressure (DBP) at Week 4 and Week 12 (subgroup analysis).

4 and Week 12, respectively, with valsartan 80- and 160-mg doses both in monotherapy and in combination therapy (Figure 3).

Analysis of treatment trends showed that at baseline, 55.91% patients were prescribed valsartan 80 mg and 44.09% patients were prescribed valsartan 160 mg, either as monotherapy or combination therapy. At Week 4, 64.30% patients required combination therapy, 3.59% were switched to another monotherapy, and 5.42% patients were switched to another combination therapy. At Week 12, 69.72% patients required combination therapy, 7.04% were switched to another monotherapy and 4.92% patients were switched to another combination therapy.

Safety

Valsartan treatment was well tolerated; about 11% patients in both the monotherapy and combination therapy groups reported AEs. A majority of the AEs were of mild to moderate intensity, were not related to the study medication, and did not result in a change in study medication. The most frequently reported AEs (≥1%) included dizziness (monotherapy vs combination, 3.58% vs 4.33%), headache (1.04% vs 1.44%), constipation (1.04% vs 0.76%) and cough (1.04% vs 0.76%). Although at Week 4, 28.89% and 22.50% AEs in the monotherapy and combination groups, respectively, were considered

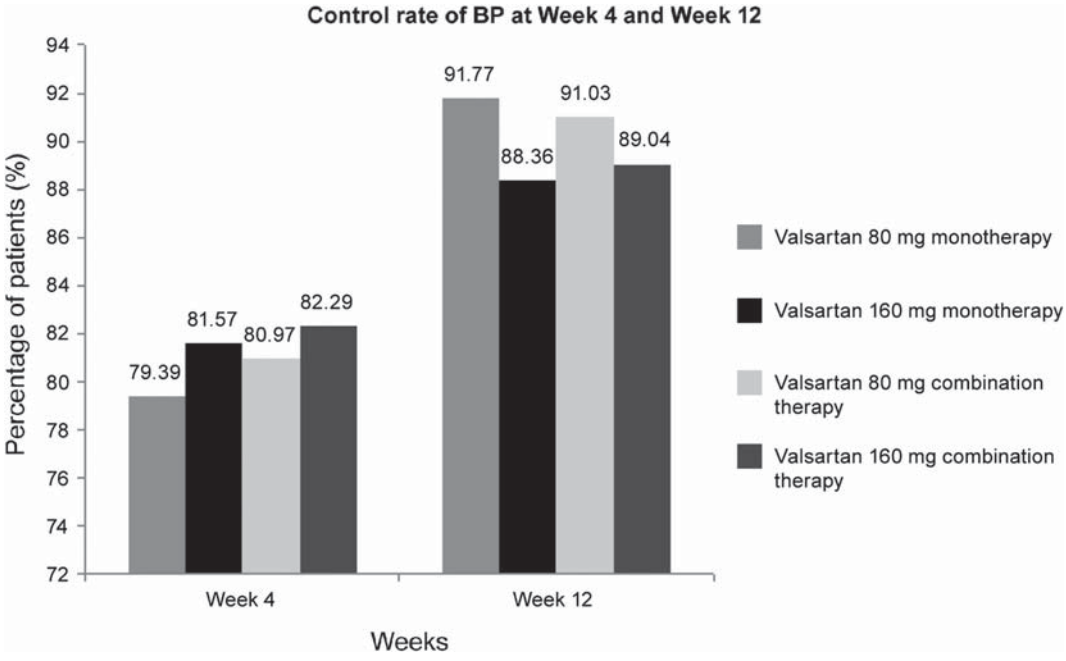

Figure 3. Blood pressure (BP) control rate at Week 4 and Week 12.

probably related to the study medication, between Week 4 and Week 12, only 5.32% and 7.78% AEs were probably related to the study medication (Table III).

Two deaths were reported in the monotherapy group; both were unrelated to valsartan treatment. SAEs were noted in five patients on valsartan monotherapy and in six patients on combination therapy. None of the SAEs in the monotherapy group was suspected to be related to the study drug. In the combination group, one case of hyperkalemia with hypovolemic shock and one case of orthostatic hypotension were suspected to be related to the study drug; however, both patients recovered completely.

Discussion

Studies have shown that ARBs are generally effective and well-tolerated antihypertensive drugs (3,18); we evaluated the efficacy and safety of valsartan as monotherapy and combination therapy in the Taiwanese population. We assessed the occurrence of dizziness both from the general and safety viewpoints. The incidence rates of dizziness (primary endpoint) with valsartan 160 mg as monotherapy and as combination therapy at Week 4 were similar. This result suggests that the incidence of dizziness did not increase with the addition of valsartan to other antihypertensive drugs. Dizziness was reported as the most frequently occurring AE in both the groups. Although not statistically significant, subjects in the combination group had a slightly higher incidence of dizziness compared with those on monotherapy (4.33% vs 3.58%). This may be related to their underlying co-morbidity or may be because of the side-effects from multiple antihypertensive drugs. Similar observations have been made previously. The incidence of dizziness with valsartan 20–160 mg was reported to be between 2.1% and 3.4% compared with 5.4% with placebo (6). A similar incidence of dizziness was reported with losartan (4%) compared with placebo (2.4%) (19). Dizziness is known to be a drug-related side-effect that occurs in about 2–4% of patients taking ARBs, which is occasionally associated with a first-dose hypotensive effect (< 1% patients) (2,4,6,17,20). Our study reported a low incidence of dizziness (3.5–4.3%) in the Taiwanese population.

Greater BP reduction was observed at Week 12 than at Week 4. Furthermore, the mean SBP reduction at Week 12 was significantly greater in the combination group than in the monotherapy group. This could be attributed to an additional antihypertensive effect from the other drug (calcium-channel blocker, diuretic, etc.) in the combination therapy. These results are in accordance with those reported by

Table III. Summary of adverse events (AEs).[a]

AEs, *n*	Monotherapy (*n* = 867)	Combination therapy (*n* = 1179)
Patients with at least one AE, *n* (%)	94 (10.84%)	124 (10.52%)
Total no. of AEs	139	170
Most commonly reported AEs (≥1%), *n* (%)		
Constipation	9 (1.04%)	9 (0.76%)
Dizziness	31 (3.58%)	51 (4.33%)
Headache	9 (1.04%)	17 (1.44%)
Cough	9 (1.04%)	9 (0.76%)

[a]Safety population; *n* (%), number (percentage) of patients experiencing AEs.

Lacourcière et al. (21), wherein significant reductions in SBP and DBP were observed with valsartan in combination therapy compared with monotherapy. A study by Calhoun et al. (22) also showed that mean reductions in BP were significantly greater with valsartan in combination therapy than as monotherapy at Week 4, with further reductions seen at Week 6. Similar results were achieved by Mallion et al. (23) at the end of 12 weeks with valsartan combination therapy vs monotherapy.

The mean age of our sample population was approximately 62 years. Previous studies have shown that the reductions in SBP and DBP were clinically and statistically significant, with SBP changes generally being higher in elderly patients than in younger subjects (10,23,24). The study also compared the efficacy of the 80- and 160-mg doses of valsartan for lowering BP at Weeks 4 and 12. The reduction in SBP from baseline was significantly greater in the 160 mg group than in the 80 mg group at both time points. Similar results have been reported by Black et al. (2), with valsartan exhibiting dose-dependent efficacy in reducing BP over the once-daily dose range of 80–320 mg. Our results are also compatible with those of Pool et al. (25), who showed that valsartan 80, 160 and 320 mg administered once a day produces dose-related decreases in SBP and DBP, with a difference from placebo of approximately 6–9/3–5 mmHg at 80–160 mg and 9/6 mmHg at 320 mg.

The proportion of patients with SBP $<$ 140 mmHg and DBP $<$ 90 mmHg at Week 12 (90%) was greater than that at Week 4 (80%). The 2002 Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) study reported a control rate of 24.3% in hypertensive patients (26). Although the TwSHHH study defined "controlled hypertension" similar to that in our study, the results should be interpreted with caution because of differences in study design and settings between both the studies. Valsartan showed twice the amount of reduction in BP in the subgroup of patients with higher baseline levels of SBP and DBP ($>$160/100 mmHg) than those with lower baseline levels in both treatment groups. Similar results have been observed in previous studies. Greater BP reduction has been reported in patients with higher baseline SBP and DBP levels ($>$ 160/100 mmHg) with valsartan therapy compared with other antihypertensive drugs (13,27,28,29). Valsartan can prove to be a valuable option in these patients either as monotherapy with the 160-mg dose or as combination therapy.

The overall safety profiles of the two groups were found to be similar. Valsartan was well tolerated with a low incidence of AEs and SAEs. Most AEs were of mild to moderate intensity and resolved. The safety and tolerability results of valsartan are known to be independent of dose and duration of treatment and are consistent regardless of age, gender and ethnic group at doses up to 320 mg/day (2). The main advantage of ARBs over ACE inhibitors is the reduced incidence of cough and angioedema (2,30,31). Dry cough was previously reported in 7.9% patients on ACE inhibitors compared with only 2.6% patients receiving valsartan therapy (2). This is agreement with our results, where cough was reported in only 1.04% and 0.76% patients in the monotherapy and combination groups, respectively.

Various trends in treatment changes at Weeks 4 and 12 were observed in this study. At Week 4, 64.30% patients required combination therapy, and 3.59% patients were switched from the 80-mg dose to the 160-mg dose as monotherapy. At Week 12, the percentage of patients requiring combination therapy increased to 69.72%, and those that switched to another monotherapy increased to 7.04%. This switch could have been because the desired results were not achieved with the existing doses. Similar observations have been made with another ARB, candesartan, which showed better results when used as an add-on (combination therapy) with other antihypertensive drugs (32). This finding seems to be in line with the ESC guidelines that suggest that effective BP control can only be achieved by a combination of at least two antihypertensive drugs (33).

The results of our study have limitations that are usually associated with observational studies, including bias in the assignment of treatment groups by the physician. Another source of bias is the absence of a control group. However, our results are relevant and important because of the large number of patients selected from the general population with few exclusion criteria and provide real-life evidence of the efficacy and safety of valsartan in Taiwanese patients with essential hypertension.

In conclusion, valsartan can be an effective treatment option for patients with essential hypertension in Taiwan.

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Disclosure

The current study was sponsored by Novartis for post-marketing surveillance of valsartan with regard to its efficacy, tolerability and safety profiles in Asia-Pacific patients. Jackson Wang is an employee of Novartis and is therefore eligible for Novartis stock and stock options. All investigators have received investigator fees from Novartis. None of the other authors has any conflict of interest to declare.

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