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Effectiveness and safety of valsartan/amlodipine in hypertensive patients with stroke

China Status II subanalysis

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Abstract

High blood pressure (BP) is a major risk factor associated with stroke in China. This is a subanalysis of patients from the China Status II study, aimed to evaluate the effectiveness and safety of valsartan/amlodipine (Val/Aml) single-pill combination (SPC) in hypertensive patients with different stroke subtypes (hemorrhagic, ischemic, or mixed).

China Status II was a multicenter, postmarketing, prospective observational study in hypertensive patients uncontrolled on monotherapy. The study was an 8-week open-label treatment period with 2 4-week follow-ups. Change in BP from baseline to weeks 4 and 8, BP control rate, and response rate at weeks 4 and 8, and safety of 8-week treatment with Val/Aml (80/5 mg) were assessed.

A total of 565 hypertensive patients with different types of stroke were analyzed in this China Status II substudy. Significant mean sitting systolic/diastolic BP (MSSBP/MSDBP) reductions from baseline to week 8 were observed across all stroke subtypes ($P < .0001$). At week 8, percentages of patients achieving MSSBP response (≥20 mm Hg reduction from baseline) were 76.3%, 74.4%, and 85.7%, MSDBP response (≥10 mm Hg reduction from baseline) were 67.8%, 65.9%, and 64.3%, and BP control (<140/90 mm Hg) were 74.6%, 80.5%, and 92.9%, in the hemorrhagic, ischemic, and mixed stroke subgroups, respectively. Adverse events (AEs) and serious AEs were reported in 5 patients (1%) and 1 patient (0.2%), respectively, in the ischemic stroke subgroup, while no AEs were reported in hemorrhagic and mixed stroke subgroups.

Val/Aml SPC was effective in hypertensive patients with different stroke subtypes and was well tolerated.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BP = blood pressure, CCB = calcium channel blocker, DALYs = disability-adjusted life years, ESC = European Society of Cardiology, ESH = European Society of Hypertension, MSDBP = mean sitting diastolic blood pressure, MSSBP = mean sitting systolic blood pressure, SD = standard deviation, SPC = single-pill combination, Val/Aml = valsartan/amlodipine.

Keywords: blood pressure, China, hypertension, single-pill combination, stroke, valsartan/amlodipine

1. Introduction

Stroke is one of the leading causes of mortality and disease burden (as measured in disability-adjusted life years [DALYs]).[1] In 2005, the global prevalence of stroke survivors (whether or not disabled as a consequence of stroke) was estimated to be 62 million, and is projected to rise to 77 million by 2030.[2] In 2010, 11.1% of all deaths worldwide were due to stroke, equally divided between hemorrhagic, ischemic, and other nonischemic stroke types,[3] and approximately 4% of global DALYs were due to stroke.[4] The majority of global stroke burden is in low- and middle-income countries, with 57% and 84% deaths and 64% and 85% DALYs lost in low- and middle-income countries, respectively.[5]

Stroke is the second most common cause of death among both urban and rural residents of China.[6] The overall incidence of stroke in China is projected to increase by 50% from 2010 to 2030. Based on an epidemiology survey of cerebrovascular disease conducted in 7 cities and 21 rural provinces in China, morbidity, mortality, and point prevalence was 219, 116, and 719 per 10 million in cities, and 185, 142, and 394 per 10 million in rural areas, respectively. Prevalence of patients with new-onset of stroke was estimated to be approximately 2 million, while nearly 1.5 million die of cerebrovascular disease.[7] Compared to developed countries, in China and many developing countries, stroke is the predominant form of cardiovascular disease and the incidence of both ischemic and of hemorrhagic stroke exceeds the incidence of ischemic heart disease.[8]

Blood pressure (BP) is the most consistent and powerful predictor of stroke. This is further supported by the fact that population mortality trends for stroke parallel those for hypertension.[9] In China, hypertension is the most important risk factor. A meta-analysis of 12 epidemiological studies with 2379 stroke cases confirmed that the overall relative risk of stroke associated with hypertension was 5.43.[10] In the INTERSTROKE study, self-reported history of hypertension was a

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significant risk factor for stroke, accounting for close to 50% of population at risk.[11] Guidelines recommend that for patients with hypertension and stroke, BP should be <140/90 mm Hg.[12–14]

Angiotensin receptor blockers (ARBs) can effectively control BP and reduce the incidence of stroke and hypertension associated with diabetes and atrial fibrillation; therefore, an ARB is recommended as a first-line treatment for stroke prevention in patients with hypertension.[15] Long-term use of calcium channel blockers (CCBs) was effective in reducing BP steadily, thereby helping to prevent atherosclerosis. CCBs can be the first choice of treatment for high BP and cerebrovascular disease.[14]

Previously conducted randomized controlled trials have shown that the ARB/CCB combination, valsartan/amlodipine (Val/Aml) (80/5 mg) single-pill combination (SPC) was superior to Val or Aml monotherapy in lowering BP and achieving BP control in Chinese patients with mild to moderate hypertension who were inadequately controlled by either monotherapy.[16] Aml and Val, 2 widely used antihypertensive drugs, have also been established to improve stroke prognosis in the VALUE study.[17,18]

China Status II, an observational study, has shown the effectiveness and safety of Val/Aml (80/5 mg) SPC in Chinese hypertensive patients uncontrolled by monotherapy.[19] The present study is a subanalysis of China Status II, evaluating the effectiveness and safety of 8-week treatment with Val/Aml SPC in hypertensive patients with stroke.

2. Materials and methods

2.1. Study design

This study was a post hoc subgroup analysis of the China Status II study based on stroke subtypes. China Status II was a multicenter, postmarketing, prospective observational study conducted in patients with essential hypertension whose BP was not adequately controlled by monotherapy. The study design and overall results have been described in detail elsewhere.[19] Briefly, the study consisted of an 8-week, open-label treatment period with 2 4-week follow-ups. An additional antihypertensive agent was added to the treatment regimens of those patients whose BP was not controlled at follow-up after 4 weeks. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice, applicable local regulations, and routine clinical outpatient practice in China. All procedures followed conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Study population

Briefly, the study population included adult Chinese patients (both male and female patients aged ≥18 years) with primary hypertension and stroke whose BP was not adequately controlled by monotherapy. Patients were categorized into 3 subgroups based on stroke subtype, namely, hemorrhagic, ischemic, or mixed stroke. All patients were administered Val/Aml (80/5 mg) SPC. Patients on antihypertensive therapy [angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs), CCBs, diuretics, or β-blockers] and those with diabetes or renal insufficiency were included. Patients were prescribed Val/Aml SPC based on the clinical judgment of the investigators according to the patient's condition and taking into consideration the package insert. Signed informed consent was obtained from all patients before study enrollment. Patients were excluded if they had any conditions that precluded administration of the drug based on the investigator's discretion. Women were also excluded if they were pregnant, lactating, or of child-bearing potential and not using adequate contraception measures. Details of inclusion/exclusion criteria, treatment assignment, and outcome measures have been previously described.[19]

2.3. Effectiveness assessments

Changes in MSSBP and MSDBP from baseline to week 4 and week 8 (study endpoint) were assessed. Also, BP control (defined as the proportion of patients achieving MSSBP/MSDBP, <140/90 mm Hg), SBP, and DBP response rates were assessed.

2.4. Safety assessments

Safety assessments included recording and measuring all AEs and vital signs in the population. The incidence of AEs was recorded at weeks 4 and 8 of the study period. Each AE was defined by its duration, severity, and relationship to the study drug.

2.5. Statistical analysis

The full analysis set and safety set for the subset of patients with stroke included patients with at least one postbaseline efficacy and safety evaluation, respectively. The full analysis set was used for all efficacy analyses.

All statistical analyses were performed using SAS Software version 9.2 (SAS Institute, Inc., Cary, NC) at 2-sided significance level (P) of <.05. Demographic and baseline variables were summarized using descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values for numeric variables, and the count number and percentage for categorical variables. Paired t test, 2-way analysis of variance, the Chi-square test, and logistic regression were used to analyze effectiveness end points, including age, height, weight, waistline, and average history of hypertension. The efficacy, tolerability, and medication compliance of Val/Aml SPC evaluated by the investigator and the patient were classified as "very good," "good," "general," and "not good."

3. Results

A total of 565 hypertensive patients with different types of stroke were analyzed in this China Status II substudy. Detailed demographic and baseline characteristics of these patients are presented in Table 1.

Of 565 patients, 59 (10.4%), 492 (87.1%), and 14 (2.5%) patients belonged to the hemorrhagic, ischemic, and mixed stroke subgroups, respectively. The average age of patients in the hemorrhagic, ischemic, and mixed stroke subgroups was 65.4 ± 13.0, 70.9 ± 11.9, and 72.2 ± 9.6 years, respectively and the proportion of men was 59.3%, 62.4%, and 85.7%, respectively. The average history of hypertension in the hemorrhagic, ischemic, and mixed stroke subgroups was 11.5 ± 10.2, 13.7 ± 10.4, and 18.1 ± 10.1 years, respectively. The mean baseline SBP was 162.0 ± 13.9, 159.9 ± 13.5, and 164.7 ± 23.0 mm Hg in the hemorrhagic, ischemic, and mixed stroke subgroups, respectively.

Most common comorbidities in the 3 stroke subgroups were coronary heart disease (CHD), diabetes, and dyslipidemia.

Table 1

Demographic and baseline characteristics of hypertensive patients with different stroke subtypes.

Characteristics	Hemorrhagic stroke (n = 59)	Ischemic stroke (n = 492)	Mixed stroke (n = 14)	P
Age, y	65.4 ± 12.9	70.9 ± 11.8	72.2 ± 9.5	.003
Gender, n (%)				.176
Male	35 (59.3)	307 (62.4)	12 (85.7)	
Female	24 (40.6)	185 (37.6)	2 (14.2)	
History of hypertension, y	11.5 ± 10.2	13.7 ± 10.4	18.1 ± 10.0	.094
Comorbidities, n (%)				
Coronary heart disease	18 (30.5)	216 (43.9)	5 (35.7)	.024
Heart failure	3 (5.0)	37 (7.5)	0 (0.0)	.042
Kidney disease	3 (5.0)	32 (6.5)	0 (0.0)	.766
Dyslipidemia	12 (20.3)	192 (39.0)	2 (14.2)	.002
Diabetes	12 (20.3)	177 (36.0)	4 (28.6)	.08
MSSBP, mm Hg	162.0 ± 13.9	159.9 ± 13.5	164.7 ± 23.0	.026
MSDBP, mm Hg	94.9 ± 12.2	89.1 ± 11.3	89.6 ± 12.7	.001
SBP substages, n (%)*				
140–159	23 (39.0)	235 (47.8)	6 (42.9)	
160–179	27 (45.8)	200 (40.7)	6 (42.9)	
>180	8 (13.6)	46 (9.3)	2 (14.3)	
Previous antihypertensive history, n (%)*				
β-blockers	2 (3.4)	25 (5.1)	0 (0.0)	
CCBs	37 (62.7)	251 (51.0)	10 (71.4)	
ACEIs	5 (8.5)	65 (13.2)	2 (14.3)	
Diuretics	1 (1.7)	12 (2.4)	0 (0.0)	
ARBs	13 (22.0)	133 (27.0)	1 (7.1)	
Others	1 (1.7)	6 (1.2)	1 (7.1)	

Data are shown as mean ± SD.

ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin renin blockers, CCBs = calcium channel blockers, MSDBP = mean sitting diastolic blood pressure, MSSBP = mean sitting systolic blood pressure, SBP = systolic blood pressure, SD = standard deviation.

* Chi-square test for categorical variables and 2-way analysis of variance for continuous variables.

Overall, 42.0%, 37.1%, and 34.5% of patients with hypertension and stroke had comorbid coronary heart disease, dyslipidemia, and diabetes, respectively. Among patients with hemorrhagic stroke, 30.5% and 20.3% of patients each had CHD and diabetes/dyslipidemia, respectively. Prevalence of comorbidities in each stroke subgroup is presented in Table 1.

ARBs (52.6%) and CCBs (25.4%) were the most widely used antihypertensive drugs across the 3 stroke subgroups. The primary reason for patients switching to Val/Aml was "BP not reaching the standard with initial monotherapy," indicated by 81.1% of patients, while 16.7% of patients switched to Val/Aml due to "BP not reaching the standard with titrated dose of monotherapy" (Table 2). Other antihypertensive drugs were added at week 4 in 2 patients (3.4%), 43 patients (8.7%), and 1 patient (7.1%) in the hemorrhagic, ischemic, and mixed stroke subgroups, respectively.

3.1. Effectiveness

Across all stroke subgroups, Val/Aml SPC resulted in significant ($P < .0001$) overall MSSBP/MSDBP reductions of 22.5/9.5 and 28.5/12.9 mm Hg from baseline to week 4 and week 8, respectively. In hemorrhagic, ischemic, and mixed stroke subgroups, Val/Aml SPC resulted in significant MSSBP/MSDBP reductions of 29.0/14.8, 27.9/12.6, and 34.7/10.2 mm Hg, by week 8 (Fig. 1).

After 4 weeks of Val/Aml SPC treatment, BP control was achieved by 50.1% of patients while after 8 weeks, BP control was attained by 80.2% of patients in the overall population (Fig. 2). BP control rates in each stroke subgroup at week 4 and week 8 are presented in Table 3. At week 4, 47.5% to 78.6% of patients achieved BP control, while the proportion of patients attaining BP control increased at week 8, with a range of 74.6% to 92.9%, across the 3 stroke subgroups.

After 4 weeks of Val/Aml SPC treatment, the rate of patients not achieving BP control was less than 9%, with 3.4%, 8.7%, and 7.1% in hemorrhagic, ischemic, and mixed stroke subgroups, respectively. At week 4, SBP response (decreasing by ≥20 mm Hg vs baseline) was achieved by 54.9%, 54.9%, and 85.7% of patients, while DBP response (decreasing by ≥10 mm Hg vs baseline) was achieved by 62.7%, 48.6%, and 57.1% of

Table 2

Reasons for switching to valsartan/amlodipine by hypertensive patients with different stroke subtypes.

Reasons	Hemorrhagic stroke (n = 59)	Ischemic stroke (n = 492)	Mixed stroke (n = 14)
BP not reaching the standard with initial monotherapy	48 (81.4)	411 (83.5)	7 (50.0)
BP not reaching the standard with titrated dose of monotherapy	10 (16.9)	70 (14.2)	7 (50.0)
Patients unable to tolerate the original treatment	0 (0.0)	7 (1.4)	0 (0.0)
Others	1 (1.7)	4 (0.8)	0 (0.0)

BP = blood pressure.

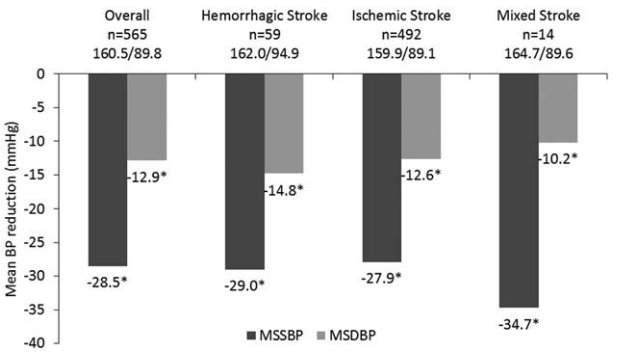

Figure 1. MSSBP and MSDBP reductions in hypertensive patients with different stroke subtypes at week 8. *$P < .0001$ versus baseline. BP = blood pressure, MSDBP = mean sitting diastolic blood pressure, MSSBP = mean sitting systolic blood pressure.

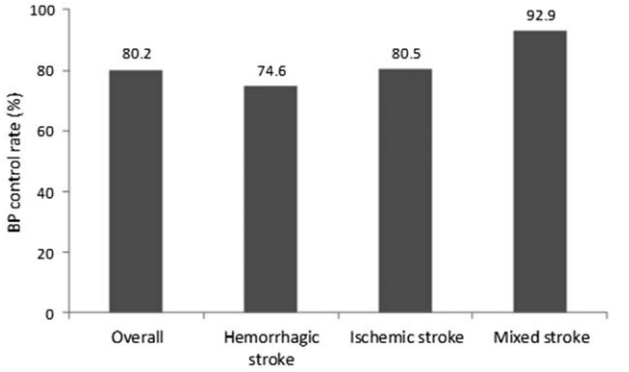

Figure 2. BP control rate (proportion of patients achieving < 140/90 mm Hg) in hypertensive patients with different stroke subtypes at week 8. BP = blood pressure.

patients in hemorrhagic, ischemic, and mixed stroke subgroups, respectively (Table 3). After 8 weeks of Val/Aml SPC treatment, SBP response increased to 76.2%, 74.4%, and 85.7% and DBP response increased to 67.8%, 65.8%, and 64.3% of patients in hemorrhagic, ischemic, and mixed stroke subgroups, respectively. After 4 weeks of Val/Aml SPC treatment, SBP and DBP control rates were 56.2% and 50.6%, respectively, and after 8 weeks, the rates were 74.6% and 66.3%, respectively, in the overall population.

3.2. Safety and tolerability

Val/Aml SPC treatment was well tolerated in the 565 patients included in the study. AEs and SAEs were reported in 5 patients (1%) and 1 patient (0.2%), respectively, in the ischemic stroke subgroup, while no AEs were reported in hemorrhagic and mixed stroke subgroups. More than 98.8% patients had higher tolerability. The majority of patients and physicians (at least 80%) across the 3 stroke subgroups rated drug compliance as "very good" (Table 4).

4. Discussion

China Status II, a multicenter, observational, real-world study, reported the effectiveness and safety of Val/Aml SPC (80/5 mg) in a very large population of Chinese patients with hypertension whose BP was inadequately controlled by monotherapy.[19] The present analysis of patients from the China Status II study stratified based on 3 stroke subtypes, confirmed the BP-lowering effectiveness and safety of Val/Aml 80/5 mg SPC in Chinese hypertensive patients with hemorrhagic, ischemic, or mixed stroke. The majority of patients achieved BP control, SBP response, and DBP response in all stroke subgroups at the study endpoint at week 8. Val/Aml SPC was safe and well-tolerated in hypertensive patients across all stroke subgroups.

Increased BP, specifically SBP > 140 mm Hg, was observed in >60% of patients during the acute phase of a hemorrhagic or an ischemic stroke.[20,21] Such increases in BP during the acute phase of a stroke have been associated with poor short-term and long-term outcomes[20,22,23] and an increased risk of early recurrence.[24] A meta-analysis of 16 randomized controlled trials comparing 95 antihypertensive drugs versus placebo in 70,664 prehypertensive patients with baseline BP ranging from 120 to 139/80 to 89 mm Hg showed that antihypertensive therapy significantly reduced the risk of stroke by 22% compared with placebo.[25] Therefore, lowering BP with antihypertensive drug in patients with hypertension during stroke would improve cardiovascular and cerebrovascular outcomes.

Table 3

Mean blood pressure, blood pressure control, and response rates at week 4 and week 8 in hemorrhagic, ischemic, and mixed stroke subgroups.

Responses	Hemorrhagic stroke	Ischemic stroke	Mixed stroke	*P*
Week 4, n	59	492	14	
MSSBP, mm Hg	139 ± 10.8	138 ± 10.7	137 ± 1 5.6	.786
MSDBP, mm Hg	83.4 ± 8.6	79.9 ± 8.7	80.4 ± 7.4	.013
Effect of decreasing SBP (decrease > 20 mm Hg vs baseline), n (%)	35 (59.3)	270 (54.9)	12 (85.7)	.063
Effect of decreasing DBP (decrease > 10 mm Hg vs baseline), n (%)	37 (62.7)	239 (48.6)	8 (57.1)	.106
BP control (<140/90 mm Hg), n (%)	28 (47.5)	247 (50.2)	11 (78.6)	.098
Week 8, n	59	492	14	
MSSBP, mm Hg	133 ± 9.8	132 ± 8.2	130 ± 7.6	.450
MSDBP, mm Hg	80.1 ± 7.2	76.5 ± 7.4	79.4 ± 5.0	<.001
Effect of decreasing SBP (decrease > 20 mm Hg vs baseline), n (%)	45 (76.2)	366 (74.4)	12 (85.7)	.608
Effect of decreasing DBP (decrease > 20 mm Hg vs baseline), n (%)	40 (67.8)	324 (65.8)	9 (64.3)	.948
BP control (<140/90 mm Hg), n (%)	44 (74.6)	396 (80.5)	13 (92.9)	.271

Data are shown as mean ± SD.

BP = blood pressure, DBP = diastolic blood pressure, MSDBP = mean sitting diastolic blood pressure, MSSBP = mean sitting systolic blood pressure, SBP = systolic blood pressure, SD = standard deviation.

Table 4

Safety and compliance in hemorrhagic, ischemic, and mixed stroke subgroups.

Characteristic	Hemorrhagic stroke (n = 59)	Ischemic stroke (n = 492)	Mixed stroke (n = 14)
AE, n (%)	0 (0.0)	5 (1.0)	0 (0.0)
SAE, n (%)	0 (0.0)	1 (0.2)	0 (0.0)
Evaluation of physicians' compliance			
Very good, n (%)	48 (81.3)	424 (85.8)	13 (92.8)
Good, n (%)	11 (18.6)	64 (12.9)	1 (7.1)
General, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Not good, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Evaluation of patients' compliance			
Very good, n (%)	53 (89.8)	436 (88.2)	12 (85.7)
Good, n (%)	6 (10.2)	52 (10.5)	2 (14.3)
General, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Not good, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event, SAE = serious adverse event.

The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) 2013 guidelines recommend antihypertensive treatment in hypertensive patients with a history of stroke or transient ischemic attack, even when initial SBP is within the range from 140 to 159 mm Hg.[13] All drug regimens (ACEI, ARB, CCB, or diuretics as monotherapies or dual/triple combination therapies) are recommended for stroke prevention, provided that BP is effectively reduced. In addition, ESC/ESH 2013 guidelines recommend initiation of combination therapy containing agents with complementary mechanisms of action (e.g., renin-angiotensin-aldosterone system blockers such as ACEIs or ARBs with CCBs and/or diuretics) in patients with markedly high baseline BP or at high cardiovascular risk. Further, SPCs are recommended as they improve compliance in patients with hypertension, usually with low adherence, thereby increasing rates of BP control and ultimately, leading to cardiovascular benefits of BP lowering.[13]

In a meta-analysis of 9 randomized clinical trials comparing antihypertensive therapies in 62,605 patients, CCBs provided more reduction in the risk of stroke compared to other classes.[26] Similar results suggesting that CCBs may have a slightly greater effectiveness on stroke prevention have also been reported by other meta-analyses and meta-regression analyses.[27,28] From experimental studies, the protective effects of CCBs on stroke might be explained by a specific role of intracellular calcium in triggering ischemic cell death. CCBs block the central neuronal calcium influx, thus reducing ischemic injury and necrosis of neurons in the ischemic brain area.[29] ARBs have also been reported to have greater cerebrovascular protective effects versus other drugs in randomized controlled trials and this was further confirmed by a meta-analysis of ~50,000 patients, where treatment with ARBs was associated with a significant reduction of stroke risk (~8%) compared with ACEIs.[30,31] ARBs exert their beneficial effects on BP lowering, cardiovascular remodeling, and stroke prevention by selectively blocking the angiotensin I receptors and allowing angiotensin II to stimulate the unoccupied angiotensin 2 receptors. This dual effect of ARBs may explain their superiority over ACEIs in stroke protection.[32]

Previous randomized clinical trials have reported significant BP-lowering effects of the Val/Aml combination therapy in patients with hypertension,[33–35] including Chinese patients with hypertension inadequately controlled by Val or Aml monotherapy.[16,36–39] Further, patients using valsartan-based SPCs are significantly more likely to achieve their BP goal than those treated with ARB-based free combinations in real-world clinical practice.[40] In a recent real-world study in Chinese patients with uncontrolled hypertension and a history of stroke, initial dual combination therapy during the first 6 months reduced stroke incidence to a greater extent than monotherapy. Also, initial therapy and maintenance therapy were mainly CCB-based (alone or in combination), and ARB/CCB combination was the dominant therapy after medication switching in patients taking combination therapy.[41] CCBs and ARBs were the most common antihypertensive drugs in our study population. In a meta-analysis of 8 RCTs in 20,451 hypertensive patients, ACEI/ARB plus CCB combination therapy was superior to other combinations in lowering the incidence of cardiovascular events, including stroke.[42] Based on the above evidence, ARB/CCB combination has the potential to reduce the risk of stroke.

The neuroprotective effect of ARBs and CCBs has been shown in a few studies. In the LIFE study conducted in hypertensive patients with left ventricular hypertrophy, losartan significantly reduced the rate of fatal and nonfatal stroke by 25%.[43] In the SCOPE study in elderly patients, candesartan-based treatment reduced nonfatal stroke by 30% and all stroke by 24% versus placebo.[44] In the ASCOT study, Aml reduced fatal and nonfatal stroke better than atenolol.[45] Nitrendipine-based treatment reduced the incidence of fatal and nonfatal stroke in elderly Chinese patients with isolated systolic hypertension.[46] An analysis of 6 actively controlled studies with Aml-based treatment showed that Aml provided more protection against stroke than other antihypertensive agent.[47] Our results show that Val/Aml SPC resulted in significant BP reductions from baseline and high BP control rates at week 8 across all stroke subtypes in patients with hypertension. The above evidence demonstrating the protective effects of Val- or Aml-based therapies against stroke, coupled with the greater BP-lowering efficacy of Val/Aml combination than either monotherapy in several studies, suggest that this combination might be an effective approach for stroke protection and prevention.

To name a few study limitations, there was no washout period in this study. The addition of treatments at week 4 might have influenced effectiveness of Val/Aml at week 8, and this impact has not been determined. Moreover, lack of a comparable group in the study introduces the potential for selection bias, which precludes generalization of the results to the entire population.

The major study limitation is the nonrandomized, open-label, single-arm design, which does not allow the comparison between treatment arm and control arm. However this study represents actual clinical practice. And it is still possible to evaluate the BP change in real world setting. A patient was prescribed the Val/Aml SPC based on the clinical judgment of the investigators. And then after 4 weeks the additional treatment was adopted when BP was not controlled at 4 weeks. Changes in MSSBP and MSDBP from baseline to week 4 and week 8 were observed. Val/Aml SPC resulted in significant overall MSSBP/MSDBP reductions from baseline to week 4 and week 8, respectively.

5. Conclusion

The present findings of the China Status II study post hoc analysis confirmed the effectiveness of Val/Aml (80/5 mg) SPC in achieving BP control and its tolerability in Chinese hypertensive patients with hemorrhagic, ischemic, or mixed stroke, in whom BP was inadequately controlled by antihypertensive monotherapy.

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