Chart review of patients receiving valsartan–amlodipine single-pill combination versus valsartan and amlodipine combination for blood pressure goal achievement and effects on the Hamilton anxiety rating/Hamilton depression rating scales

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Abstract
This study aimed to compare the Hamilton anxiety rating/Hamilton depression rating (HAMA/HAMD) scale scores and blood pressure (BP) goal achievement associated with the use of valsartan–amlodipine single-pill combinations (SPCs) versus valsartan and amlodipine combination in adult hypertensive patients.

A total of 476 hypertensive patients were randomly assigned into the SPC (valsartan–amlodipine) and control (valsartan and amlodipine combination) groups. All patients had an uncontrolled BP (160–179/100–109 mm Hg). BP goal was <140/90 mm Hg. Cox proportional hazards regression analysis was used to analyze the likelihood of HAMA/HAMD scales, SPCs, control group, and daily dosage number. Kaplan–Meier analysis was used to estimate the rates of BP goal achievement over time among the 2 groups.

A total of 476 patients were included in the study, and 439 patients completed the follow-up and received the index drug therapy. There was a significant difference in BP between the 2 groups on days 28, 42, and 56. Patients who received SPCs had a significantly higher rate of BP goal achievement over time (P = .000). The average HAMD scores in the SPC and control groups were 5.54 and 6.49 and 6.06 and 6.21 on days 28 and 56, respectively. The average HAMA scores in the SPC and control groups were 7.41 and 7.13 and 7.90 and 8.01 on days 28 and 56, respectively. The means of HAMD and HAMA scores were 5.826 and 7.13 and 7.90 and 8.01 on days 28 and 56, respectively. The higher the HAMA/HAMD scores, the lower was the BP goal achievement. The number of drugs taken by the patients was associated with the HAMA and HAMD scores. There was no significant difference between HAMA scores of patients taking 1 tablet daily (7.22 ± 1.885) and those taking two-tablets daily (7.38 ± 1.953) (P = .408). However, when these scores were compared to those of patients taking 4 tablets daily (8.08 ± 2.285), a significant difference was observed (P = .000, P = .000).

Hypertensive patients treated with valsartan–amlodipine SPCs were significantly more likely to achieve BP goal and have lesser HAMA/HAMD scores compared to patients treated with valsartan and amlodipine combination.

Abbreviations: ABPM = ambulatory blood pressure monitoring, BMI = body mass index, BP = blood pressure, CVD = cardiovascular disease, DBP = diastolic blood pressure, HAMA = Hamilton anxiety scale, HAMD = Hamilton depression scale, SBP = systolic blood pressure, SPCs = single-pill combinations.

Keywords: amlodipine, BP goal achievement, HAMA, HAMD, single-pill combinations, valsartan

1. Introduction
Observational studies have demonstrated graded associations between hypertension and increased cardiovascular disease (CVD) risk.[1] In China, there are approximately 270 million adults aged ≥18 years with systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg,[2] with a hypertension control rate of <20%. Hypertension results from a complex interaction of genes and environmental factors. A single antihypertensive drug can only target 1 aspect. Hence, current guidelines recommend more stringent blood pressure (BP) targets. Increasing the dose of monotherapy produces minimal additional BP-lowering effects and may increase the risk of adverse effects, while changing from 1 monotherapy to another is frustrating, time-consuming, and often ineffective.[3] Hence, the recent guidelines have recommended initiating treatment with drug combinations.[4,5] Hypertensive patients treated with single-pill combinations (SPCs) are significantly more likely to achieve the BP goal compared to patients treated with a combination of 2 drugs in the real-world clinical practice.[6] However, the mechanism for this hypothesis remains unclear.
An epidemiological study showed that depression and anxiety play significant roles in hypertensive patients. These abnormal psychological and emotional responses increase BP and lead to poor BP control rate. The amount and variety of antihypertensive drugs may influence patients’ psychological emotion. Patients will feel more anxious when they take several drugs. SPCs reduce the number of drugs taken, which is one of the possible reasons why SPC has a better effect than a combination of 2 drugs.

The study was designed to compare the effects of the most commonly prescribed SPC (Exforge) versus amlodipine combined with valsartan as the first-line treatment of hypertensive patients to observe their effects on controlling hypertension, anxiety, and depression. We expect to provide sufficient evidence to guide effective BP control with SPCs.

1.1. Study sample

This study was based on a chart review of hypertensive patients who received SPC or amlodipine combined with valsartan. Previous studies have shown that SPC group achieved a 15% higher standard rate compared to the free combination therapy group. Group sample sizes of 190 in group 1 and 190 in group 2 achieved 90.055% power to detect a difference between the group proportions of 0.1470. The proportion in group 1 (the treatment group) was assumed to be 0.5000 under the null hypothesis and 0.6470 under the alternative hypothesis. The proportion in group 2 (the control group) was 0.5000. The test statistics used was the 1-sided Z-test with unpooled variance. P-value of .05 was considered statistically significant. The rate of dropouts was <20%. In this study, we collected the necessary information on 238 patients in each group.

Patients were considered eligible for this study if they met the following inclusion criteria:

1. patients who were at least 18 years or older and under 65 years old (women of childbearing age need to adapt adequate contraceptive methods and are willing to use contraception within 1 month after the end of the trial);
2. patients who have high BP (SBP should be 160–179 mm Hg and/or DBP should be 100–109 mm Hg) between January 1, 2016, and October 1, 2018;
3. patients who did not receive antihypertensive drugs in 1 month;
4. patients who are able to perform a timely 2-month follow-up; and
5. patients who have no dementia and mental retardation, are not deaf-mute, have no other speech communication disorders and cognitive impairment, and agree to participate in the experimental study.

Exclusion criteria were as follows:

1. patients who have severe liver and kidney dysfunction,
2. patients who have diabetes mellitus or other diseases requiring drugs,
3. patients who have a history of major mental trauma in 3 months,
4. patients who have anxiety, depression, and other mental illnesses,
5. patients who have family history of mental illness,
6. patients who have alcoholism and drug addiction,
7. patients who have participated in other drug experimenters in the last month, and
8. patients who have acute and critical hypertension that requires emergency treatment.

1.1.1. Random grouping method. To ensure the balance of the sample size across the 2 groups, a stratified random sampling framework was used. A total of 476 serial numbers were generated using the Statistical Package for the Social Sciences software (fixed value, 19,720,609). According to the random number, the serial numbers were divided into the SPC group and the control group. Hypertensive patients who met the selected criteria were randomly grouped according to their visiting serial numbers.

2. Methods

2.1. Measures for BP goal achievement

BP goal achievement was defined based on the guidelines from the European Society of Hypertension/European Society of Cardiology (ESH/ESC) practice guidelines for the management of arterial hypertension. Adult hypertensive patients without diabetes, chronic renal disease, or coronary heart disease had SBP <140 mm Hg and diastolic BP <90 mm Hg. BP was measured by 1 nurse in the consultation room. The investigators were trained on how to perform the study procedures at the beginning of the trial. The study methods were based on the guidelines from the Joint National Commission 7 and the American Heart Association/American College of Cardiology.

The SPC group received valsartan and amlodipine tablets (l) (Exforge, Novartis, Basel, Switzerland 80mg/5mg/tablet) as antihypertensive drugs. One tablet was taken orally once a day. If the patient’s achieved the BP goal in the 2-week follow-up visit, the dose would remain unchanged. If the patient’s BP was above the BP goal, he/she was prescribed 2 tablets orally once a day. The control group received valsartan capsules ( Diovan, Novartis, 80 mg/capsule) and amlodipine tablets (Norvasc, Pfizer, 5 mg/tablet) as antihypertensive drugs, both taken orally once a day. If the patient’s BP goal was achieved in the 2-week follow-up visit, the dose would remain unchanged. If the patient’s BP was above the BP goal, the dose was changed to the following: valsartan capsules 160 mg and amlodipine tablets 10 mg, both taken orally once a day (Fig. 1).

All patients were assessed using Omnibus Risk Estimator before the start of treatment. They received aspirin/statins if necessary.

All patients received healthy lifestyle education and counseling, including dietary sodium restriction, moderate consumption of alcohol, healthy balanced diet consumption, weight reduction, regular physical activity, and smoking cessation, when they were diagnosed with hypertension.

BP was monitored in all patients in the consultation room by the same nurse on days 14, 28, 42, and 56 after index antihypertension treatment. The Hamilton depression rating 17 (HAM-D-17) and Hamilton anxiety rating (HAMA) scores were measured by 2 psychologists before receiving antihypertensive drugs and again on days 28 and 56. Information regarding patient’s age, sex, race/ethnicity, history of hypertension, baseline BP before the index therapy initiation, comorbidities, and body mass index (BMI) were also collected.

2.2. Statistical analysis

Normally distributed continuous variables were expressed as means ± standard deviation of the mean (standard error of the
mean), abnormally distributed continuous variables were expressed as median (interquartile range), and categorical variables were expressed as number (percentage).

For equivalent variables with a normal distribution, the independent Student \( t \) test was used to compare the 2 groups. The Mann–Whitney \( U \) test was used to compare categorical variables and abnormal distributional variables between the 2 groups. One-way analysis of variance and the Kruskal–Wallis test were used to compare multiple groups.

During the observational period, crude rate of BP goal achievement was calculated for the SPC versus the control group, respectively, defined as the time-period from the day after the index therapy initiation to BP goal achievement date or a censoring event, whichever came first. Additionally, Kaplan–Meier analysis was used to estimate the rates of BP goal achievement over time among the 2 groups. Goal achievement rates were compared using the log-rank test. Cox proportional hazards regression analysis was used to analyze the effect of an array of variables on 56-day BP goal achievement rate. Patients were censored at the earliest date of the following events:

1. discontinuation of the index therapy,
2. administration of other antihypertensive drugs, and
3. loss to follow-up.

Log-rank tests were used to compare the rates of BP goal achievement between patients in the 2 groups.
A 2-sided P-value < .05 was considered statistically significant; confidence intervals were set at 95%. Statistical analyses were performed using the SPSS version 17.0.

3. Results

A total of 476 patients were included in the study. Among these patients, 238 received SPC (valsartan and amlopidine tablets [I]), while the remaining 238 received valsartan capsules in combination with amlopidine tablets.

The baseline demographics, BMI, baseline BP, daily salt intake, exercise and smoking status, lipid profile, family history of hypertension, duration of hypertension, and educational level were similar between patients treated with SPC and those treated with a combination of antihypertensive drugs. The mean age and mean education time of the overall sample was 55 years and 9 years, respectively (Table 1). The average SBP of the SPC and control groups was 26.57 mm Hg and 27.89 mm Hg above the BP goal, respectively (Table 1). The average SBP in the SPC and control groups was 26.57 mm Hg and 27.89 mm Hg above the BP goal, respectively (Table 1). The average DBP in the SPC and control groups was 9.04 mm Hg and 9.29 mm Hg above the DBP goal, respectively. The mean HAMD and HAMA scores were 4.43 and 5.54, respectively.

There were a total of 439 patients who finished the follow-up and received drugs as part of the index therapy initiation. Moreover, 16 patients in the SPC group were excluded (4 patients did not receive the index therapies defined in this study, 8 patients lost to follow-up, 4 patients were treated for other diseases during the study). A total of 21 patients in the control group were excluded (12 patients did not receive the index therapies defined in this study, 6 patients lost to follow-up, 3 patients were treated for other diseases during the study). Furthermore, 427 patients received aspirin due to atherosclerotic CVD risk (210 in the SPC group and 217 in the control group). A total of 161 patients received statin (79 in the SPC group and 217 in the control group). There were 67 patients who received atorvastatin and 12 patients who received rosuvastatin in the SPC group, and there were 73 patients who received atorvastatin and 9 patients who received rosuvastatin in the control group.

The average BP of the SPC and control groups was 150.21/91.06 mm Hg and 151.28/91.29 mm Hg on day 14 (t = 1.064, P = .288; t = .341, P = .733), with no significant difference between the 2 groups. However, there was a statistically significant difference in BP between the 2 groups on day 28 (t = 5.585, P = .000; t = 2.703, P = .000), 42 (t = 6.368, P = .000; t = 6.576, P = .000), and 56 (t = 9.849, P = .000; t = 8.876, P = .000) (Table 2).

3.1. BP goal achievement

Overall, there were a total of 221 patients (162 patients in the SPC group and 59 patients in the control group) who achieved BP goal during the observation period. The results from the Kaplan–Meier analyses showed that compared with patients on the control group, patients who received SPC had a significantly higher rate of achieving BP goal over time (P = .000, log-rank test) (Fig. 2). There were a total of 7, 69, 122, and 162 patients and 5, 33, 49, and 59 patients in the SPC and control groups who achieved the BP goal on days 14, 28, 42, and 56 after the index therapy initiation, respectively.

3.2. HAMD and HAMA scores

The average HAMA score increased and had a significant difference after the index therapy initiation. The average scores of
all patients were 7.65 ± 2.155 and 7.57 ± 2.056 on days 28 and 56, respectively ($F = 175.625, P = .000$). The average HAMA score increased and had a significant difference after the index therapy initiation. The average HAMD scores of all patients were 5.8 ± 2.046 and 5.85 ± 2.024 on days 28 and 56, respectively ($F = 88.621, P = .000$) (Table 3).

The average HAMD and HAMA scores on the SPC group and the control group were different after the index therapy initiation.
Table 3
HAMD and HAMA scale on patients.

| (I) Time | (J) Time | MD (I-J) | SD | P  | Lower | Upper |
|---------|---------|--------|----|----|-------|-------|
| HAMA    | 1       | 28     | -2.107  | 0.127 | .000 | -2.36 | -1.96 |
|         | 56      | 1      | 2.107   | 0.127 | .000 | 1.86  | 2.36  |
|         | 28      | 56     | 0.086   | 0.130 | .510 | -0.17 | 0.34  |
|         | 28      | 56     | 2.022   | 0.129 | .000 | 1.77  | 2.27  |
| HAMD    | 1       | 28     | -1.363  | 0.120 | .000 | -1.60 | -1.13 |
|         | 56      | 1      | -1.413  | 0.122 | .000 | -1.65 | -1.17 |
|         | 28      | 56     | -0.050  | 0.123 | .682 | -0.29 | 0.19  |
|         | 28      | 56     | 1.415   | 0.122 | .000 | 1.17  | 1.65  |

Comparison was performed using LSD (least-significant difference).
D = confidence interval; HAMA = Hamilton anxiety scale; HAMD = Hamilton depression scale; MD = mean difference; SD = standard deviation.

Table 4
HAMD and HAMA scale on 2 group.

| Time, d | Group   | n   | HAMD (M ± SD) | HAMA (M ± SD) | t     | P    |
|---------|---------|-----|---------------|---------------|-------|------|
| 1       | SPC     | 238 | 4.44 ± 1.415  | 5.52 ± 1.619  | 0.033 | .974 |
|         | Control | 238 | 4.43 ± 1.376  | 5.57 ± 1.576  | 0.316 | .755 |
| 28      | SPC     | 231 | 5.94 ± 1.195  | 7.41 ± 2.043  | 2.766 | .006 |
|         | Control | 228 | 6.06 ± 2.144  | 7.90 ± 2.240  | 2.460 | .014 |
| 56      | SPC     | 223 | 5.49 ± 1.857  | 7.13 ± 1.788  | 3.779 | .000 |
|         | Control | 217 | 6.21 ± 2.126  | 8.01 ± 2.217  | 4.561 | .000 |

Comparison was performed using Student t test (continuous variables).
HAMA = Hamilton anxiety scale; HAMD = Hamilton depression scale. SPC = single pill combination.
The scale on SPC group versus control group.

(Table 4). The average HAMD scores in the SPC and control groups were 5.54 and 5.49 (t = 0.2823, P = .7779) and 6.06 and 6.21 (t = 0.7407, P = .4592) on days 28 and 56, respectively. Moreover, the average HAMA scores in the SPC and control groups were 7.41 and 7.13 (t = 1.5318, P = .1214) and 7.90 and 8.01 (t = 0.5024, P = .6030) on days 28 and 56, respectively. There was no significant difference between the scores on days 28 and 56 between the 2 groups. However, the HAMD and HAMA scores were different on these days between the 2 groups after the index therapy initiation (Table 4).

3.3. HAMD and HAMA scores and BP goal achievement

The HAMD and HAMA risk factor estimates derived from Cox proportional hazard models are presented in Table 5. The average HAMD and HAMA scores were 5.826 and 7.614, respectively. The higher the HAMD and HAMA scores, the lower the BP goal achievement. The number of drugs taken by the patients was associated with the HAMA and HAMD scores (Table 6). There was no significant difference between the HAMA scores of patients receiving 1-tablet daily (n = 169, 7.22 ± 1.885) and those receiving 2-tablets daily (n = 387, 7.38 ± 1.953) (P = .408). However, when these scores were compared with those of patients receiving 4-tablets daily (n = 342, 8.08 ± 2.285) a significant difference was observed (P = .000, P = .000). HAMD scores of patients receiving 1-tablet daily (n = 169, 5.06 ± 1.678) and those receiving 2-tablets daily (n = 387, 5.65 ± 1.924) differed significantly (P = .002) from those of patients receiving 4-tablets daily (n = 342, 6.40 ± 2.155) (P = .000, P = .000).

Table 5
Cox proportional hazard model of blood pressure goal achievement comparing HAMD/HAMA scale and daily dosage.

| Variable   | Hazard rate | SE     | Wald   | P-value | Exp (B) | 95% CI          |
|------------|-------------|--------|--------|---------|---------|-----------------|
| HAMA       | 0.092       | 0.039  | 10.106 | .012    | 1.097   | (0.533, 0.670)  |
| HAMD       | 0.123       | 0.037  | 6.252  | .001    | 0.884   | (0.820, 0.954)  |
| Daily dosage | -0.514     | 0.058  | 77.440 | .000    | 0.598   | (0.533, 0.670)  |

Comparison was performed using Cox proportional hazard model.
B = beta, CI = confidence interval, Exp = exponential, HAMA = Hamilton anxiety scale, HAMD = Hamilton depression scale, SE = standard error.
The scale on SPC group versus control group. *P < .05.
4. Discussion

In this recent study, adherence to treatment was significantly influenced by the number of drugs that a patient received for the treatment of hypertension. The 2018 ESH/ESC Practice Guidelines recommend the use of SPC therapy as an initial therapy for most patients because reducing the number of administered drugs improves adherence and increases the BP control rate.

Although the actual drug composition is similar, the efficacy of the SPC and combination drug is different in real-world clinical practice. Considering the effects of hypertension, patients often have negative emotions such as anxiety and depression, leading to BP fluctuation and further affecting drugs’ efficacy. Patients taking more than 2 antihypertensive drugs have a high incidence of depression. The dosage, quantity, and frequency of the drugs will directly affect drug adherence. The effect of drugs on anxiety and depression may be one of the reasons regarding the difference in efficacy between the SPC and combination drug. There are many factors associated with the incidence and outcome of cardiovascular events, such as BP variability. Change in BP variability is reproducible and can interact with patients’ neurological function. The nervous states can also cause BP fluctuations.

HAMA and HAMD scales are clinical scales that assess anxiety and depression. The HAMA and HAMD scores significantly increased in a short period of time after patients received treatment for hypertension. We observed that the BP control rate, a rate that was achieved in the SPC group, was significantly higher than that in the control group. To eliminate interference, we selected patients who did not receive other drugs and who had no comorbidities. After the index therapy initiation, both the HAMA and HAMD scores were higher. With the increase of observation time, the score did not change significantly between days 28 and 56. Although the HAMA/HAMD scores remained within the normal range and patients did not require antianxiety/antidepressant treatment, this study suggested that the diagnosis and treatment of hypertension affect the mental and psychological status of patients. With prolonged diagnosis and treatment, patient’s score stabilized, which is probably due to the patient’s acceptance regarding the nature of hypertension. The HAMA/HAMD scores of the SPC group were lower than that of the control group after the index therapy initiation. The number of drugs taken per day and the HAMA/HAMD scores were associated with BP goal achievement. However, there was no significant difference in the scores of 1 tablet and 2 tablets daily dosage. Moreover, a 4 tablet daily dosage increased the HAMA/HAMD scores significantly. The difference between HAMA/HAMD scores and BP goal achievement in the 2 groups may be related to daily dosage.

5. Conclusion

Hypertensive patients who were treated with valsartan–amlodipine SPCs were significantly more likely to achieve BP goal compared to patients who were treated with valsartan in combination with amlodipine. The HAMA/HAMD score in the SPC group was lesser than that in the control group.

6. Study limitations

Hypertensive patients usually had other complicated diseases, specifically diabetes, and hyperlipidemia. The use of selection criteria means that the results of the study are not generalizable for all hypertensive patients. Several factors such as diet, exercise, and smoking affected the HAMA/HAMD scores. This study only involves BP measurement, rather than ambulatory blood pressure monitoring (ABPM). The ABPM will be more accurate and convincing.

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