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ORIGINAL ARTICLE

# The effect of fixed-dose combination of valsartan and amlodipine on nighttime blood pressure in patients with non-dipper hypertension

## Amlodipin/valsartan sabit doz kombinasyonunun non-dipper hipertansif hastalarda gece saatlerindeki kan basıncı üzerine etkisi

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## ABSTRACT

***Objective:*** Failure to decrease blood pressure (BP) during the night is associated with higher cardiovascular (CV) morbidity and mortality. There is strong evidence that fixed-dose combinations (FDCs) of antihypertensive agents are associated with significant improvement and non-significant adverse effects. The aim of the present study was to evaluate whether FDC affected nocturnal BP favorably in patients with uncontrolled, non-dipper hypertension (HT).

***Methods:*** All non-dipper hypertensives were either newly diagnosed with stage 2–3 HT or had HT uncontrolled with monotherapy. Patients (n=195) were consecutively assigned to 4 treatment groups: FDC of valsartan/amlodipine (160/5 mg), free-drug combination of valsartan 160 mg and amlodipine 5 mg, amlodipine 10 mg, and valsartan 320 mg. Ambulatory blood pressure monitoring (ABPM) was repeated at 4$^{th}$ and 8$^{th}$ week.

***Results:*** Average 24-h (24-hour) and nocturnal BP were similar among the groups at baseline evaluation, and had significantly decreased by the fourth week of treatment. However, BP continued to decrease only slightly between the 4$^{th}$ and 8$^{th}$ weeks in the valsartan and amlodipine monotherapy groups, but continued to decrease significantly in both combination groups. After 4 weeks, day-night BP difference and day-night BP % change were significantly elevated in the combination and valsartan groups. Between the 4$^{th}$ and 8$^{th}$ weeks, however, day-night BP difference and day-night BP % change continued to rise only in the FDC group, nearly reducing to baseline levels in the free-drug combination and valsartan groups. An additional 2.2 mmHg decrease was observed in the FDC group, compared to the free-drug combination group.

***Conclusion:*** In non-dipper HT, FDC of valsartan and amlodipine improved diurnal-nocturnal ratio of BP and provided 24-h coverage.

## ÖZET

***Amaç:*** Gece saatlerinde kan basıncında (KB) beklenen düşmenin olmaması kardiyovasküler olay gelişimi ve sağ kalımla ilişkilidir. Antihipertansif ilaçların sabit doz kombinasyonlarının (SDK) ciddi yan etkiye yol açmaksızın hastanın tedaviye uyumunda belirgin bir düzelme sağladığı yönünde güçlü kanıtlar vardır. Bu çalışmada, SKD'lerin kan basıncı kontrolü sağlanmamış "non-dipper" hipertansiyonlu olgularda gece KB düşmesi üzerine olumlu etkilerinin olup olmadığı araştırıldı.

***Yöntemler:*** Çalışma, yeni tanı konmuş evre 2–3 hipertansif olgular ya da tek antihipertansif ilaç kullanmakta olup KB kontrolü sağlanamamış olgulardan oluşturuldu. Olgular ardışık olarak dört gruba alındı: Valsartan/amlodipin SDK (160/5 mg); valsartan 160 mg + amlodipin 5 mg tekli ilaç kombinasyonu; amlodipin 10 mg; valsartan 320 mg. İlk değerlendirmede tüm hastalara ayaktan KB ölçümü yapıldı ve ölçümler tedavinin 4. ve 8. haftasında tekrarlandı.

***Bulgular:*** Bazal değerlendirmede elde edilen 24 saatlik ortalama gece kan basınçları tüm gruplarda benzerdi ve 4 haftalık tedavi sonrası tüm gruplarda anlamlı düşüş sağlandı; 4–8 haftalık tedavi periyodunda her iki kombinasyon grubunda anlamlı düşüş devam ederken amlodipine ve valsartan grubunda hafif bir düşüş saptandı. İlk 4 haftalık tedavi sonrası gündüz-gece KB farkı ve gündüz-gece KB değişiklik oranı (%) her iki kombinasyon grubunda ve valsartan grubunda anlamlı olarak yükseldi. Artışlar SDK grubunda 4–8 haftalık periyotta da devam etti fakat tekli ilaç kombinasyonu ve valsartan grubunda bu farklar azaldı ve neredeyse bazal değerlendirmedeki değerlere döndü. Tekli ilaç kombinasyonu ile karşılaştırıldığında, SDK grubunda 2.2 mmHg'lik ek bir düşüş gözlendi.

***Sonuç:*** Non-dipper hipertansiyonlularda valsartan/amlodipine SDK gündüz/gece KB oranını düzeltir ve 24-saat etkili KB düşüşü sağlar.

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**Abbreviations:**

| | |
|---|---|
| *24-h* | *24-hour* |
| *ABPM* | *Ambulatory blood pressure monitoring* |
| *BP* | *Blood pressure* |
| *CI* | *Confidence interval* |
| *CV* | *Cardiovascular* |
| *DBP* | *Diastolic blood pressure* |
| *FDC* | *Fixed-dose combination* |
| *HT* | *Hypertension* |
| *SBP* | *Systolic blood pressure* |

Strong evidence has been presented that elevated blood pressure (BP) is the major modifiable risk contributor to ischemic heart disease, stroke-related mortality, and global mortality.[1–3] In addition, large randomized trials have clearly demonstrated that reduction of BP reduces risk of cardiovascular (CV) morbidity and mortality.[4] While effective antihypertensive agents are available worldwide, a single antihypertensive agent achieves target BP level (<140/90 mmHg) in only 20–30% of hypertension cases.[5,6] Recent studies have revealed that target BP can be achieved in a majority of hypertension cases with combination therapy involving 2 or more antihypertensive agents. Accordingly, recent guidelines recommend as first-line therapy a combination of at least 2 drugs in order to improve BP control in most hypertensive patients.[7–9]

Hypertensive patients are categorized as dippers or non-dippers according to reduction in nocturnal BP of ≥ or <10%, respectively. While antihypertensive treatment affects both daytime and nighttime BP, the prognostic value of nocturnal BP is superior.[3,10] Therefore, 24-hour (24-h) ambulatory blood pressure monitoring (ABPM) is useful, both in diagnosis and during treatment.

Currently, fixed-dose combinations (FDCs) of 2 or 3 drugs have become very popular because of the many advantages, including better patient adherence, superior alterations to pharmacodynamics, longer duration of action, lower clinical and metabolic adverse effects, broader spectrum of response, and more prompt achievement of target BP.[11] Confirming these advantages, recent studies have shown that treatment with FDC of angiotensin-receptor blocker and hydrochlorothiazide provides greater clinical and ambulatory BP reduction than treatment with component monotherapies.[12,13] While there is strong evidence that FDCs of antihypertensive agents are associated with significant improvement in compliance, and non-significant beneficial trends in BP and adverse effects, compared with free-drug combinations, no study to date has compared the effects of FDCs with free-drug combinations of antihypertensives on non-dipping BP.

The aim of the present study was to investigate whether FDC of valsartan and amlodipine achieved more significant decrease in non-dipping BP than free-drug combination of valsartan and amlodipine or their component monotherapies.

## METHODS

### Study population

Between February 2011 and December 2012, a total of 1281 sustained essential hypertensive subjects were evaluated in an office setting, and 491 subjects newly diagnosed with stage 2–3 hypertension (HT; n=296, 60%) or uncontrolled HT with monotherapy (n=195, 40%) were screened for baseline evaluation. All subjects with uncontrolled HT had received antihypertensive treatment for at least 6 months. All subjects underwent ABPM. Subjects with white-coat HT, white-coat effect, and dipping BP were excluded; 232 subjects with non-dipping BP were included. A total of 37 subjects with non-dipping BP were excluded due to other exclusion criteria; 29 were excluded due to current use of amlodipine or valsartan, 4 due to excessive alcohol usage, and 4 due to history of thyroid disease. A total of 195 eligible patients with non-dipping BP were consecutively assigned to 4 treatment groups: FDC of valsartan/amlodipine (160/5 mg), free-drug combination of valsartan 160 mg and amlodipine 5 mg, amlodipine 10 mg, and valsartan 320 mg. Patients were encouraged to take their medication regularly in the morning (between 08:00 and 10:00). Inclusion criteria were 30–75 years of age, absence of secondary causes of HT, and no history of CV disease. Exclusion criteria were current use of amlodipine or valsartan, excessive alcohol consumption (>120 g/day), and concomitant systemic disease other than diabetes mellitus, including hemolytic, rheumatic, hepatic, and renal diseases or possible chronic renal disease (glomerular filtration rate <60 mL/min per 1.73 $m^2$). Written informed consent was obtained from all participants, and study protocol was approved by the institutional ethics committee.

### Blood pressure measurement in an office setting

According to current guidelines,[7–9] office BP was measured with mercury sphygmomanometer, and first and fifth Korotkoff sounds were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP). Appropriate cuff size was chosen for

each subject's arm circumference. BP was measured 3 times after 15 minutes of rest in a seated position by skilled, trained physicians. Measurements were repeated after 48 hours and the average of all measurements was recorded. Physical examination included measurement of height (cm) and weight (kg), and a resting 12-lead electrocardiogram was recorded. Subjects with BP above 140/90 mmHg were considered uncontrolled hypertensives.

## Ambulatory blood pressure monitoring

Noninvasive 24-h ABPM was performed with Tracker NIBP2 portable compact digital recorder (Del Mar Reynolds Medical Ltd., Hertford, UK), and analyzed using CardioNavigator customized analytical software (Spacelabs Healthcare Inc., Snoqualmie, WA, USA). Each subject wore an ABPM device with an appropriately sized cuff for a single 24-hour period. Device was programmed to inflate and record BP at pre-specified intervals (every 15 minutes during daytime hours and every 30 minutes during nighttime hours), providing approximately 80 BP recordings during the 24-h period. Display was deactivated to prevent distraction of subjects by BP readings.

ABPM records included BP measurements, heart rate, mean arterial pressure, BP load, and summary statistics for the entire 24-h period. If at least 80% of BP readings were valid, ABPM record was considered satisfactory and used for further analysis. Daytime and nighttime periods were set according to sleep schedules of subjects. To test reproducibility, ABPM was repeated after 4 or 5 days in 12 participants (8 subjects with uncontrolled HT and 4 subjects with newly diagnosed stage 2 HT). Correlation coefficients for 24-h SBP, DBP, and mean blood pressure (MBP) were 0.942, 0.936, and 0.954, respectively.

## Patient classification

All patients used prescribed antihypertensive medications during ABPM. Based on current guidelines,[7–9]

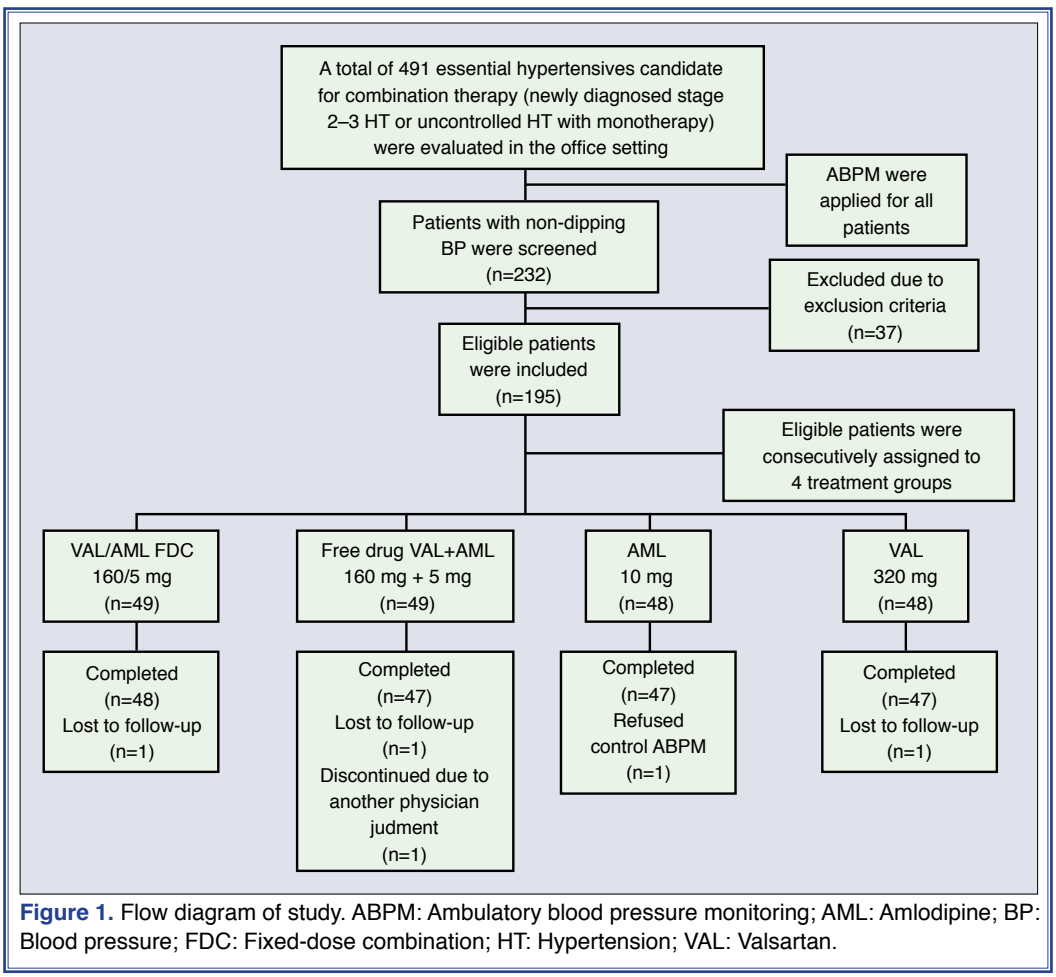


**Figure 1.** Flow diagram of study. ABPM: Ambulatory blood pressure monitoring; AML: Amlodipine; BP: Blood pressure; FDC: Fixed-dose combination; HT: Hypertension; VAL: Valsartan.

**Table 1. Demographic characteristics, office blood pressure, risk factors for coronary artery disease, laboratory findings, and medications**

| | VAL/AML single pill FDC | VAL+AML free drug combination | AML alone | VAL alone |
|---|---|---|---|---|
| Number | 48 | 47 | 47 | 47 |
| Age (year) | 53.6±11.3 | 52.6±10.0 | 50.4±10.0 | 52.2±10.1 |
| Male/female (n/n) | 26/22 | 27/20 | 26/21 | 27/20 |
| Body-mass index (kg/m$^2$) | 29.3±3.6 | 29.7±3.6 | 28.9 ± 4.1 | 28.8±3.2 |
| Body-mass index ≥30 kg/m$^2$ (%) | 58 | 57 | 55 | 62 |
| Diabetes mellitus (%) | 17 | 13 | 15 | 13 |
| Dyslipidemia (%) | 21 | 20 | 23 | 20 |
| Current smoker (%) | 10 | 6 | 15 | 13 |
| Newly diagnosed hypertension (%) | 60 | 57 | 62 | 60 |
| Duration of hypertension (month) | 32.6±16.2 | 30.8±14.7 | 31.9±14.9 | 30.9±12.9 |
| Office systolic blood pressure (mmHg) | 160.7± 7.6 | 160.4±6.9 | 163.9±13.8 | 161.5±8.9 |
| Office diastolic blood pressure (mmHg) | 95.6±10.1 | 93.2±9.7 | 93.3±7.9 | 91.5±10.2 |
| Heart rate (bpm) | 78.6±11.3 | 79.6±9.8 | 79.7±9.7 | 79.2±9.1 |
| ACEI/ARB usage (%) | 23 | 17 | 21 | 17 |
| Beta blocker usage (%) | 6 | 4 | 8 | 8 |
| Calcium channel blocker usage (%) | 6 | 4 | 4 | 4 |
| Diuretic usage (%) | 4 | 4 | 2 | 2 |
| Oral anti-diabetic usage (%) | 15 | 11 | 11 | 13 |
| Statin usage (%) | 21 | 20 | 23 | 20 |
| Creatinine (mg/dL) | 0.89±0.21 | 0.91±0.19 | 0.90±0.18 | 0.89±0.16 |
| Glucose (mg/dL) | 102.1±9.0 | 101.8±13.2 | 101.6±9.7 | 102.1±21.2 |
| Total cholesterol (mg/dL) | 188.8±34.5 | 190.9±32.3 | 189.3±32.1 | 188.5±40.5 |
| High-density lipoprotein cholesterol (mg/dL) | 46.3±13.4 | 46.7±8.2 | 47.3±12.0 | 46.0±9.4 |
| Low-density lipoprotein cholesterol (mg/dL) | 114.6±30.1 | 110.6±30.2 | 110.9±28.3 | 112.8±36.5 |
| Triglyceride (mg/dL) | 145.1±86.0 | 154.9±79.2 | 151.9±85.3 | 154.9±81.3 |

VAL: Valsartan; AML: Amlodipine; FDC: fixed-dose combination; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

and according to 24-h ABPM results, patients with SBP ≥140 mmHg and/or DBP ≥90 mmHg during office visit, average 24-h SBP ≥130 mmHg and/or DBP ≥80 mmHg, and average daytime SBP >135 mmHg and/or DBP ≥85 mmHg, or average nighttime SBP ≥120 mmHg and/or DBP ≥70 mmHg recorded by ABPM were diagnosed with true HT; those with white-coat HT were excluded. Patients were then diagnosed with dipping or non-dipper HT, according to reduction of nocturnal BP ≥ or <10%, respectively.

## Power calculation and statistical analysis

Based on previous data,[7–9] it is estimated that HT affects 30% of the adult population aged 30–75, that BP is controlled in 30–50% of hypertensive patients, and that at least half the population with uncontrolled HT have non-dipping BP. Using G*Power (version 3.0.10, Franz Faul, Universität Kiel, Germany), it was calculated that a total of 180 subjects were needed in order to fill the 4 groups at α err prob <0.05 and 1–β err prob of 0.85. Excess of this number was recruited to minimize risk of type II error.

Analyses were performed using SPSS software (version 9.0; SPSS Inc., Chicago, IL, USA). Categorical variables were defined as percentage, and numeric data were expressed as mean±SD. Categorical variables among groups were compared using chi-square

**Table 2. Data from ambulatory blood pressure monitoring of groups**

| | VAL/AML single pill FDC | VAL+AML free drug combination | AML alone | VAL alone |
|---|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD | Mean±SD |
| Average 24-h systolic blood pressure | 136.1±9.0 | 135.1±10.1 | 137.0±13.0 | 134.5±10.6 |
| Average 24-h diastolic blood pressure | 82.5±10.1 | 83.7±7.6 | 83.8±8.9 | 82.3±8.0 |
| Average 24-h mean blood pressure | 98.4±11.9 | 100.0±8.8 | 100.0±10.2 | 96.4±10.3 |
| 24-h mean heart rate (bpm) | 77.5±9.4 | 76.7±8.7 | 77.4±8.1 | 78.1±10.2 |
| Average daytime systolic blood pressure | 138.8±10.9 | 137.6±11.8 | 139.0±13.5 | 137.5±12.5 |
| Average daytime diastolic blood pressure | 84.3±10.5 | 86.1±8.2 | 85.7±9.5 | 83.2±9.8 |
| Average daytime mean blood pressure | 100.6±12.6 | 102.1±9.8 | 102.4±10.8 | 98.6±11.0 |
| Daytime mean heart rate (bpm) | 81.2±9.6 | 80.7±9.5 | 81.1±8.7 | 82.0±10.8 |
| Average nighttime systolic blood pressure | 129.7±7.5 | 129.6±7.4 | 129.5±11.8 | 128.8±8.5 |
| Average nighttime diastolic blood pressure | 78.2±11.2 | 79.4±6.9 | 77.1±10.6 | 77.0±8.4 |
| Average nighttime mean blood pressure | 93.6±11.9 | 95.5±7.9 | 92.9±11.3 | 91.8±9.5 |
| Nighttime mean heart rate (bpm) | 70.5±11.1 | 69.3±8.9 | 69.1±8.3 | 71.0±9.3 |
| Day-night difference in systolic blood pressure | 9.1±3.1 | 8.0±2.4 | 9.6±2.7 | 8.7±3.5 |
| Day-night change in systolic blood pressure (%) | 6.2±3.3 | 5.5±1.7 | 6.6±3.2 | 5.9±2.5 |
| Day-night difference in diastolic blood pressure | 6.1±2.8 | 6.7±1.8 | 8.6±2.7 | 6.2±3.3 |
| Day-night change in diastolic blood pressure (%) | 7.1±2.9 | 7.5±2.0 | 9.8±3.2 | 7.1±2.5 |
| Day-night difference in mean blood pressure | 7.0±2.4 | 6.6±1.9 | 9.5±3.1 | 6.8±2.9 |
| Day-night change in mean blood pressure (%) | 6.7±2.4 | 6.2±1.7 | 9.0±3.0 | 6.5±2.8 |

VAL: Valsartan; AML: Amlodipine; FDC: fixed-dose combination; SD: Standard deviation.

analysis. One-way analysis of variance was used to compare continuous variables, followed by Tukey's test or Kruskal-Wallis test (for comparison of a characteristic across groups if it did not have a normal distribution, such as triglyceride). Comparison analyses of ABPM before and after treatment were performed using paired t-test. A p value less than 0.05 was considered significant.

## RESULTS

### Clinical characteristics of study population

According to ambulatory BP measurements, 195 eligible patients with non-dipping BP were consecutively assigned to 4 treatment groups: FDC of valsartan/amlodipine (160/5 mg), free-drug combination of valsartan 160 mg and amlodipine 5 mg, amlodipine 10 mg, and valsartan 320 mg. ABPM was repeated during 4$^{th}$ and 8$^{th}$ weeks. Five patients did not complete the study (Figure 1). Baseline characteristics and risk factors for CV disease are presented in Table 1. Age, gender, body mass index, duration of HT, office BP measurements, heart rate, smoking status, laboratory findings, and medication status were comparable among the groups, as were percentages of subjects with newly diagnosed HT, diabetes mellitus, and dyslipidemia.

### Ambulatory blood pressure monitoring analysis

Heart rates, and average 24-h, daytime, and nighttime BP measurements were similar among groups at baseline evaluation. Day-night difference and day-night % change in SBP, DBP, and MBP did not significantly differ among groups at baseline evaluation (Table 2).

Average 24-h SBP significantly decreased (from 136.1±9.0, 135.1±10.1, 136.9±13.0, 134.5±4.6 mmHg to 126.6±9.7, 128.2±14.6, 129.4±10.9, 127.0±9.5 mmHg; FDC, free-drug combination, amlodipine, and valsartan groups, respectively, p<0.001 for all), as did nighttime SBP (from 129.7±7.5, 129.6±7.4, 129.5±11.8, 128.8±8.5 mmHg to 120.1±10.8, 120.2±16.1, 123.4±10.6, 118.1±11.5 mmHg; FDC,

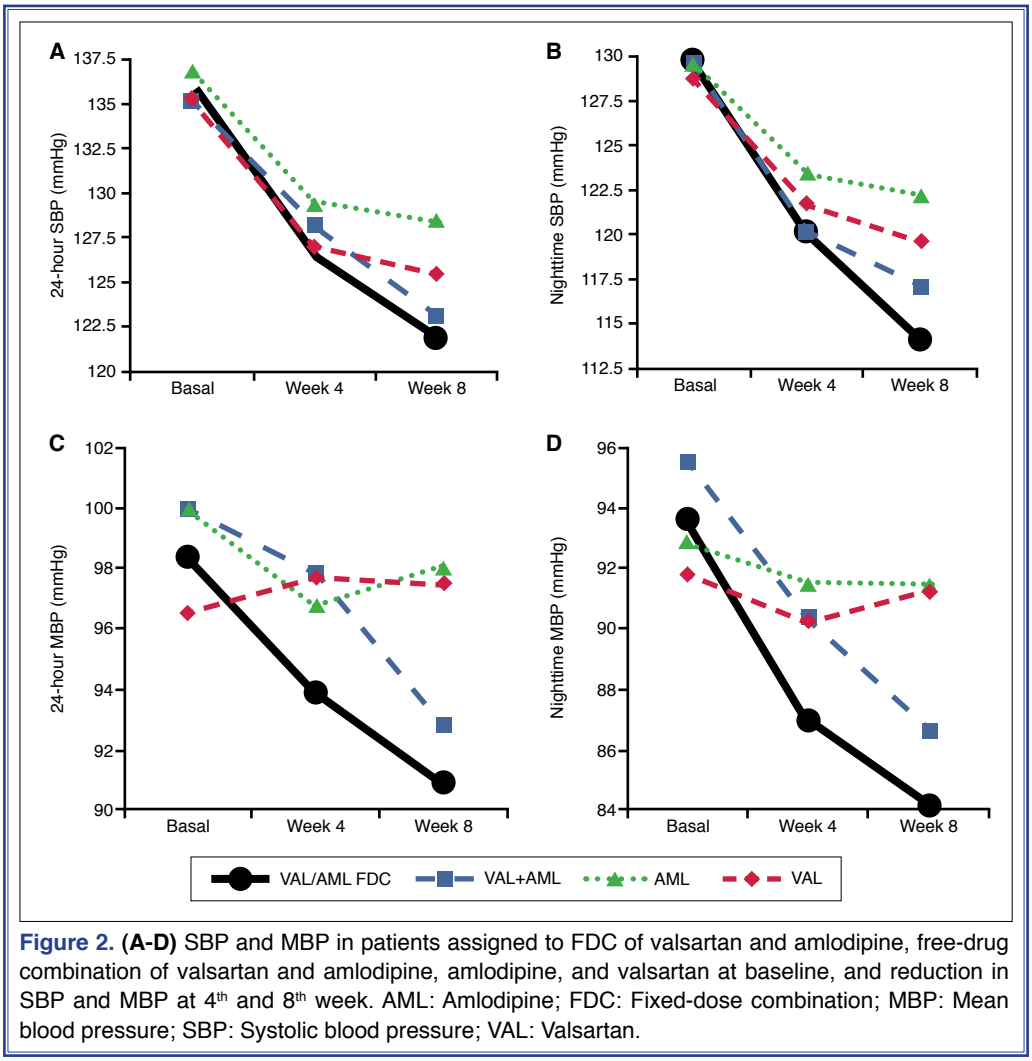


**Figure 2. (A-D)** SBP and MBP in patients assigned to FDC of valsartan and amlodipine, free-drug combination of valsartan and amlodipine, amlodipine, and valsartan at baseline, and reduction in SBP and MBP at 4th and 8th week. AML: Amlodipine; FDC: Fixed-dose combination; MBP: Mean blood pressure; SBP: Systolic blood pressure; VAL: Valsartan.

free-drug combination, amlodipine, and valsartan groups, respectively, p<0.001 for all), and did not significantly differ among the groups after fourth week of treatment (Figure 2a, b). Average 24-h and nighttime SBP measurements decreased slightly between 4th and 8th weeks in valsartan and amlodipine monotherapy groups, but continued to decrease significantly in both combination groups (24-h SBP to 121.9±8.4 and 123.1±10.0 mmHg, and nocturnal SBP to 114.0±8.7 and 117.1±11.5 mmHg; FDC and free-drug combination, respectively, p<0.001 *vs* baseline and p<0.01 *vs* week 4 measurement) (Figure 2a, b). Similarly, average 24-h and nighttime MBP measurements significantly decreased after fourth week and continued to decrease between 4th and 8th weeks in both combination groups (Figure 2c, d). However, in the valsartan group, average 24-h MBP slightly increased, then remained unchanged between 4th and 8th weeks. In the amlodipine group, average 24-h MBP significantly decreased after fourth week and increased slightly between 4th and 8th weeks (Figure 2c). At no time did nighttime MBP significantly change (Figure 2d).

## Analysis of non-dipping blood pressure pattern

Day-night differences and day-night % changes in BP measurements were comparable among groups at baseline evaluation (Table 2). However, they were significantly elevated after the fourth week in the combination and valsartan groups (SBP from 9.1±3.1 [6.2±3.3%], 8.0±2.4 [5.5±1.7%], 8.7±3.5 [5.9±2.5%] mmHg to 9.4±3.8 [7.2±2.5%], 11.1±4.1 [8.5±3.1%], 12.1±5.5 [9.2±3.6%] mmHg, and MBP from 7.0±2.4 [6.7±2.4%], 6.6±1.9 [6.2±1.7%], 6.8±2.9 [6.5±2.8%] mmHg to 9.1±3.6 [9.3±3.7%], 10.1±3.3 [10.0±3.5%], 10.4±4.2 [10.0±3.9%] mmHg; FDC, free-drug combination, and valsartan groups, respectively, p<0.05

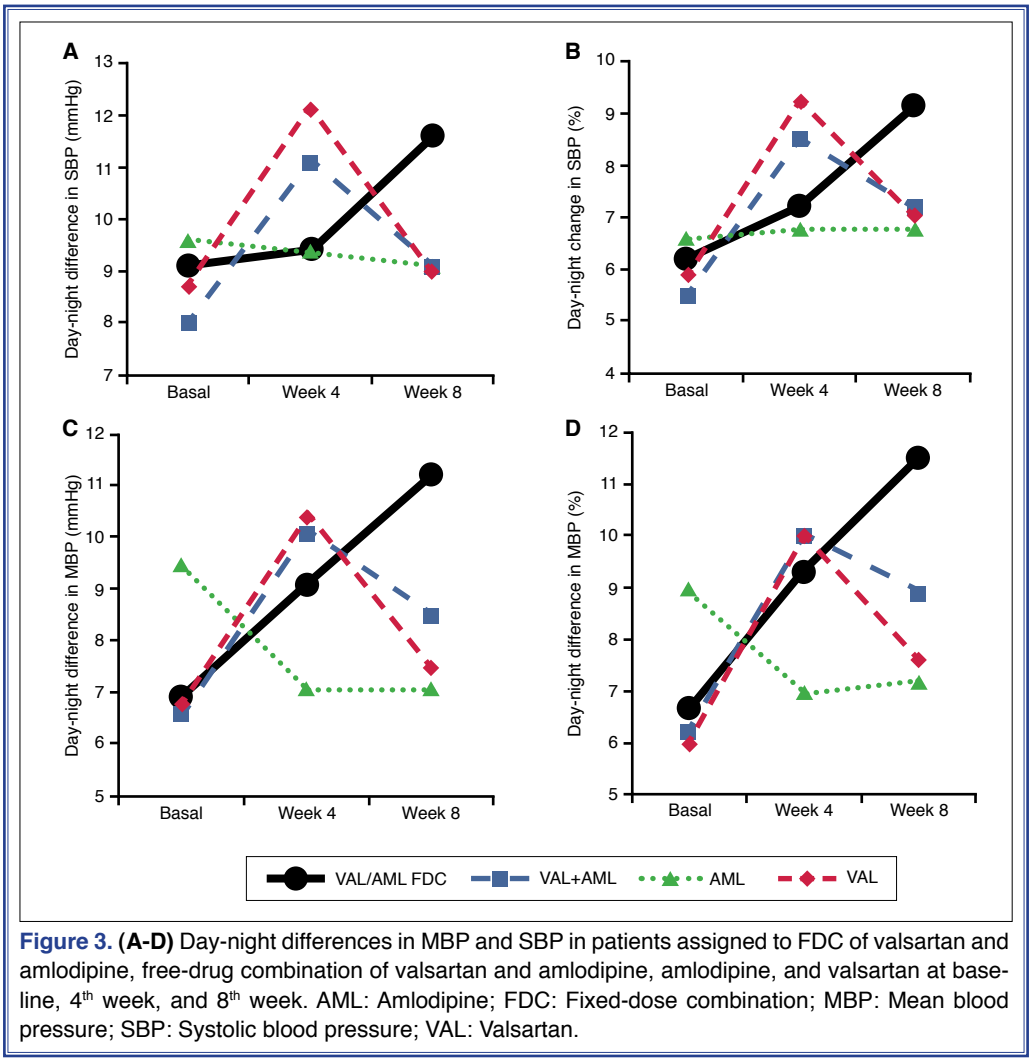


**Figure 3.** **(A-D)** Day-night differences in MBP and SBP in patients assigned to FDC of valsartan and amlodipine, free-drug combination of valsartan and amlodipine, amlodipine, and valsartan at baseline, 4th week, and 8th week. AML: Amlodipine; FDC: Fixed-dose combination; MBP: Mean blood pressure; SBP: Systolic blood pressure; VAL: Valsartan.

*vs* baseline for all groups). However, BP measurements of the amlodipine group were not significantly changed (Figure 3). While BP measurements of the FDC group continued to rise between the 4th and 8th weeks (SBP from 9.4±3.8 [7.2±2.5%] to 11.6±3.9 [9.1±2.8%] mmHg, and MBP from 9.1±3.6 [9.3±3.7%] to 11.2±3.5 [11.5±3.4%] mmHg, $p<0.001$ *vs* baseline, $p<0.01$ *vs* week 4), these measurements were significantly reduced in the free-drug combination and valsartan groups during the same period, returning nearly to baseline levels (Figure 3).

### Adherence, safety, and adverse events

Patient adherence was evaluated at 3-month intervals by returned pill count. Adherence to therapy was excellent, above 98% in all groups. At each visit, patients were asked to report adverse events, and presence of peripheral edema was evaluated. Peripheral edema occurred most frequently, and was significantly more common among patients in the amlodipine group (19%). In addition, cough was frequently reported, being slightly, but not significantly, more prevalent among patients in the the valsartan group (11%), the free-drug combination group (9%), and the FDC group (6%) than among those in the amlodipine group (4%). Several temporary adverse events including dizziness, headache, and weakness were also reported. However, all treatment regimens were tolerated well, with no serious adverse events or clinically notable abnormal laboratory findings that would require discontinuation or interruption of treatment.

## DISCUSSION

The present study was the first to assess the efficacy of an angiotensin-receptor blocker and calcium-chan-

nel blocker FDC on non-dipping BP in patients with newly diagnosed stage 2 or uncontrolled HT. FDC of valsartan and amlodipine produced robust reductions in nighttime SBP, DBP, and MBP during 8-week treatment period. Results also indicated that FDC of valsartan and amlodipine provided 24-h coverage when taken upon awakening and more effectively reduced 24-h SBP, DBP, and MBP than single daily dose of 320 mg valsartan or 10 mg amlodipine. Although there was no statistically significant difference between the FDC and the same daily doses of valsartan and amlodipine in free-drug combination, the approximate 2.2 mmHg additional decrease in 24-h SBP observed in the FDC group is of clinical importance, as it has been clearly demonstrated that a reduction in SBP as low as 3 mmHg is associated with an 8% reduction in stroke-related mortality, a 5% reduction in coronary artery disease-related mortality, and a 4% reduction in total mortality.[14,15]

Current guidelines recommend combination therapy of 2 drugs for the majority of hypertensive patients with ≥20/10 mmHg above target BP. Currently, many single-pill FDCs are available in the US and most European countries. It has been shown that FDC of valsartan and amlodipine has an excellent safety profile, and is effective and well-tolerated in patients with HT that is not well-controlled with valsartan monotherapy.[16] Allemann et al.[17] reported that BP control (<140/90 mmHg, <130/80 mmHg in diabetics) was achieved in 72.7% (95% confidence interval [CI], 68.6–76.9) of patients receiving valsartan/amlodipine FDC of 160/5 mg, and in 74.8% (95% CI, 70.8–78.9) of those receiving valsartan/amlodipine FDC of 160/10 mg during a 16-week treatment period. Similarly, in 2 multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies that evaluated the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension, Philipp et al.[18] suggested that the combination was associated with significantly greater reductions in BP from baseline, compared with monotherapy or placebo. In addition, incidence of peripheral edema was significantly lower with combination therapy than with amlodipine monotherapy. Schrader et al.[19] found that combination of valsartan and amlodipine 160/5 mg had improved antihypertensive effect and better tolerability profile than high-dose (10 mg) amlodipine in patients who did not respond to amlodipine 5 mg. The present study also demonstrated the beneficial effects of fixed-dose and free-drug combinations of valsartan and amlodipine on BP control, compared to corresponding monotherapies.

More frequent administration of FDC in recent years may have achieved better BP control by improving patient compliance, compared to separate administration of antihypertensive agents.[20] However, while many studies have shown that FDC of valsartan and amlodipine more effectively reduces BP than use of component monotherapies, and that administration of FDC is associated with lower discontinuation and better compliance than administration of free-drug combination,[20] data comparing FDC of valsartan and amlodipine with free-drug combination has been limited.

The present study also compared the effects of fixed-dose and free-drug combinations of valsartan and amlodipine on 24-h BP measurements obtained by ABPM in uncontrolled, non-dipper HT. Although the difference in 24-h BP reduction between FDC and the same daily doses of valsartan and amlodipine in free-drug combination were not statistically significant, the approximate 2.2 mmHg additional decrease in 24-h SBP of patients taking FDC is clinically important, as even small differences in BP reduction (about 4/2 mmHg) are associated with significant changes in incidence of stroke, all-cause mortality, and time to first cardiac event.[21]

Office BP measurements remain the cornerstone for decisions regarding treatment of HT, and most therapeutic trials have focused on lowering office BP measurements. However, it has been well-documented that ABPM and home BP monitoring aid in more accurate HT diagnosis and better prediction of CV events.[2] In addition, measurements obtained by ABPM are more closely related to indices of preclinical target organ damage than those obtained during an office visit.[2,4] Furthermore, ABPM can allow for the exclusion of white-coat effect and detect masked HT. While home BP measurements share similar advantages with ABPM, only 24-h ABPM offers a complete range of data. Nighttime BP measurements are of particular significance, as they are considered to be better indicators of CV risk and mortality than those obtained during the day.[3,22] Both SBP and DBP typically decrease about 15—25% at night. A nocturnal BP decrease of <10% is classified as non-dipping, and

failure to decrease BP is associated with a 2.5-times-higher risk of CV events.[23]

However, Kozan et al. recently reported lack of BP control at night and early morning in a majority of patients with BP under control according to office measurements.[24] Studies have shown that evening administration of long-acting antihypertensive agents provides greater reduction of nocturnal BP than morning administration.[25,26] Results from a Heart Outcomes Prevention Evaluation sub-study in which patients were evaluated with ABPM indicated significant BP reduction, primarily during the night, when ramipril was administered at bedtime.[27] The authors reported that an 8% increase in diurnal-nocturnal BP ratio was associated with beneficial effects on CV mortality and morbidity. In a prospective 9.2-year follow-up study, Ohkubo et al.[28] demonstrated that diminished nocturnal decline in SBP was a predictor of CV risk in the general population, independent of 24-h BP overload. The authors suggested that each 5% decrease in decline of nocturnal SBP in hypertensive patients was associated with an approximate 31% increased risk of CV mortality. Furthermore, it was reported that the association between nocturnal BP and CV mortality was also observed in normotensive subjects with an average 118/69 mmHg 24-h BP. In their study, 24-h BP values were similar among groups; however, subjects with diminished nocturnal SBP decline had increased risk of CV mortality, compared to those with nocturnal SBP decline of at least 10%. Moreover, non-dipper normotensive subjects had a relative hazard of CV mortality (2.16) similar to that of subjects with dipper HT (2.37).[32] In addition, it was recently demonstrated that an increase in diurnal-nocturnal ratio of BP was markedly correlated with a significant decrease in urinary albumin excretion.[29] Accordingly, the present study was focused on reduction of nocturnal BP in particular, using diverse antihypertensive regimens. In patients with uncontrolled, non-dipper HT, FDC of valsartan and amlodipine had more beneficial effects on nocturnal BP reduction and diurnal-nocturnal BP ratio than the same daily doses as free-drug combination or the use of corresponding monotherapies.

In conclusion, it is suggested that FDC of 2 antihypertensive agents is associated with significant improvement in 24-h BP. Data also showed that FDCs may have beneficial effects on control of nocturnal BP, compared to component monotherapies and corresponding free-drug regimens. Further well-designed and well-conducted randomized studies are needed to refute or corroborate these findings. If they are correct, there are wide-ranging potential benefits to prevention of CV outcomes. Therefore, assuming the existence of no major cost disadvantages, the use of FDCs should be encouraged in the management of HT, particularly in non-dipping HT.

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*Keywords:* Amlodipine; ambulatory blood pressure; non-dipper; fixed dose combination; valsartan.

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