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# The role of ambulatory blood pressure monitoring compared with clinic and home blood pressure measures in evaluating moderate versus intensive treatment of hypertension with amlodipine/valsartan for patients uncontrolled on angiotensin receptor blocker monotherapy

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## Abstract

**Objectives—**Ambulatory blood pressure monitoring (ABPM) has greater predictive value than office blood pressure (BP) with respect to hypertension-related target-organ damage and morbidity. ABPM in a subset of 80 patients from the Exforge Target Achievement trial (*N*= 728) was used to compare the efficacy of intensive-treatment and moderate-treatment regimens of amlodipine/valsartan, and to determine whether treatment differences could be better assessed with ABPM than with office or home BP. Home BP was measured on the morning of clinic visits to minimize differences that timing might have on home versus office BP measures.

**Methods—**A 12-week randomized, double-blind study in which hypertensive patients earlier uncontrolled (mean sitting systolic BP≥150 and <200 mmHg) on angiotensin receptor blocker monotherapy (other than valsartan) after 28 days or more (*N*=728) were randomized to amlodipine/valsartan treatment [10/320mg (intensive) or 5/160mg (moderate)]. Treatment-naive patients (in previous 28 days) or patients who failed on a nonangiotensin receptor blocker agent underwent a 28-day run-in period with a 20-mg or 40-mg dose of olmesartan, respectively.

**Results—**Significantly greater 24-h ABP reductions from baseline to week 4 (primary time point) were observed with intensive versus moderate treatment (least-square mean systolic/diastolic BP reduction of −16.2/ −10.1 vs. −9.5/−6.5 mmHg; *P*=0.0024/*P*=0.010 for least-square mean difference). Similarly, a significantly greater proportion of patients receiving an intensive treatment achieved ambulatory BP goal (<130/80 mmHg) at week 4 than did those receiving a



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moderate treatment ($P$=0.040). Treatment-group differences did not reach statistical significance for these end points when measured by office and home BP.

**Conclusion—**In this first randomized trial evaluating the effects of intensive versus moderate dosing of the combination of amlodipine/valsartan, our data suggest that ABPM was a better method for assessing between-treatment differences than clinic or home BP recordings, although measurement of home BP as a single recording was a limitation of our trial.

### Keywords

ambulatory blood pressure monitoring; amlodipine; combination therapy; hydrochlorothiazide; hypertension; valsartan

## Introduction

The use of 24-h ambulatory blood pressure monitoring (ABPM) has greatly improved the ability to assess the time course of antihypertensive treatment-associated lowering of blood pressure (BP) throughout the dosing interval. Multiple measurements throughout the day are capable of capturing fluctuations missed by BP sampling once daily in the clinic or at home and of minimizing the impact of placebo and 'white-coat hypertension' effects [1]. ABPM can reveal relationships between plasma drug levels and therapeutic effect, identify times of day during which a medication is less effective, provide insight into the impact of missed doses, and detect variability in BP during the night and early morning (at the end of the dosing interval in most treated patients), which could have a considerable influence on cardiovascular outcomes [1–3]. ABPM has greater predictive value than office or home BP with respect to hypertension-related targetorgan damage and morbid events [3–7].

For all these reasons, ABPM is particularly useful for the evaluation of antihypertensive drugs in clinical trials [8]. A few clinical studies have used ABPM to assess the efficacy of an angiotensin receptor blocker (ARB) in combination with another antihypertensive [9–12]; however, none of these studies has compared ABPM with both clinic and home BP measurements. The Exforge Target Achievement (EXTRA) trial compared the efficacy of intensive and moderate treatment regimens with amlodipine/valsartan using clinic BP measurements [13]. Both regimens were well tolerated, with a low incidence of adverse events. In this prespecified analysis of the EXTRA data, in a subset of patients, we determined whether the efficacy of intensive versus moderate treatment with amlodipine/valsartan could be better assessed with ABPM than with clinic or home BP recording.

## Materials and methods

Methods for the EXTRA trial have been described earlier in detail [13] and are briefly summarized here. The study protocol was approved by the ethics committee or institutional review board at each center, and the study was conducted according to the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

### Patients

Men and women who were aged 18 years or older and who had a documented diagnosis of hypertension, with a mean sitting systolic BP (MSSBP) of 150mmHg or more and less than 200mmHg were included in this study. Participants were treatment-naive or had uncontrolled BP (as defined earlier) with ARB monotherapy, other than valsartan, or with any single antihypertensive agent, other than an ARB. Patients with uncontrolled, treated type 2 diabetes [glycosylated hemoglobin (HbA1c) >8.5%] and with a history of dialysis or nephrotic syndrome and an estimated glomerular filtration rate of less than 50ml/min/ 1.73

$m^2$ (Modification of Diet in Renal Disease method) at 3 months before screening, or with other significant concomitant diseases, were excluded. In addition, individuals who had an arm circumference of greater than 42cm, who worked at night or on rotational or alternating shifts, or who were currently experiencing atrial fibrillation were excluded from the ABPM substudy. At screening, serum sodium concentrations had to be at least 135mEq/l and potassium levels had to be between 3.5 and 5.5mEq/l (inclusive). Women were postmenopausal, surgically sterile, or using an adequate method of contraception.

## Study design

This 12-week, randomized, double-blind, parallel-group study was conducted at 140 centers in the USA. Patients earlier uncontrolled on ARB monotherapy (other than valsartan) after 28 days or more (MSSBP≥150 and < 200mmHg) were randomized directly to receive double-blind treatment. Patients who were naive to antihypertensive therapy within the earlier 28 days entered the open-label run-in phase, during which they received a 20-mg dose of olmesartan for 28 days. Patients who failed with any single agent other than an ARB also entered the open-label run-in phase, during which they received a 40-mg dose of olmesartan for 28 days. Thereafter, olmesartan-treated patients (20 or 40 mg) whose BP remained uncontrolled and who satisfied the other inclusion/exclusion criteria were randomized to double-blind treatment.

As shown in Fig. 1, patients randomized to intensive treatment received 5/320mg amlodipine/valsartan through week 2, 10/320mg amlodipine/valsartan from weeks 2 to 4, and 10/320/12.5 mg amlodipine/valsartan/hydrochlorothiazide (HCTZ) from weeks 4 to 8. Patients randomized to moderate treatment received 5/160 mg amlodipine/valsartan through week 4 and 5/160/12.5mg amlodipine/valsartan/HCTZ from weeks 4 to 8. In both groups, physicians had the option of including an additional dose of 12.5mg of HCTZ at week 8 (i.e. total dose of HCTZ was 25mg) if patients had an MSSBP of more than 140mmHg. Nonstudy antihypertensive agents, or other concomitant medications likely to interfere with the evaluation of study medication, were prohibited during the trial. Use of sildenafil and vardenafil was prohibited within 24 h and tadalafil within 48 h before any scheduled visit.

## Ambulatory blood pressure monitoring

ABPM was conducted in prespecified patients included from 20 sites participating in the ABPM substudy. This subset of patients attended three additional clinic visits (24h before weeks 0, 4, and 12) during which the ABPM device (Model SpaceLabs 90207, Issaquah, Washington, USA) was used. Patients were instructed to wear the ABPM device for 24 h thereafter, during which BP readings were collected at regular intervals. For the ABPM patients, analyses were based on the intent-to-treat population (i.e. all patients with a valid baseline and ≥ 1 postbaseline ABPM measurements) and included changes from baseline to weeks 4 and 12 in the following: 24-h ambulatory systolic BP (ASBP), 24-h ambulatory diastolic BP (ADBP), daytime (06:00 h–22:00 h) ASBP and ADBP, night-time (22:00 h–06:00h) ASBP and ADBP, and last 6-h ASBP and ADBP. In addition, the proportion of patients achieving the 24-h ambulatory BP (ABP) goal (<130/80 mmHg) was determined.

## Clinic blood pressure

An automated BP monitor (Model #HEM-705CP; Omron, Schaumburg, Illinois, USA) was used for office BP measurements, in accordance with the guidelines of the British Hypertension Society [14]. At each visit, three sitting BP measurements were obtained at an interval of 2 min or more. The mean of these three measurements was used as the average sitting BP. Results presented here [changes from baseline to weeks 4 and 12 in clinic systolic BP (SBP) and diastolic BP (DBP), proportion of patients achieving the clinic BP

goal (< 140/90 mmHg)] are for the subset of patients who participated in the ABPM substudy.

### Home blood pressure

All patients who underwent ABPM were given a home BP monitor (same model as that used for clinic BP) and trained in its use. Patients were instructed to measure their home BP three times during the morning of their appointment to have the ABPM device applied. Home BP recordings were done in the morning of clinic visits. Changes from baseline to weeks 4 and 12 in home SBP and DBP, and the proportion of patients achieving the home BP goal (<140/90 mmHg), are reported for the same subset of patients participating in the ABPM study.

### Statistical methods

Sample size determination and primary statistical analyses for this study were presented earlier [13]. For the ABPM substudy analyses described here, demographic and baseline characteristics were analyzed using a two-sample *t*-test, $\chi^2$-test, or Fisher's exact test. Within-treatment changes from baseline to each visit (weeks 4 and 12) in ABP, clinic BP, and home BP in the ABPM substudy population were analyzed using a paired *t*-test, and between-treatment differences were analyzed using an analysis of covariance model. On the basis of this fitted model, a two-sided 95% confidence interval (CI) for mean treatment difference between the treatment regimens and the associated *P* value was obtained. The least-square mean of each treatment arm was also estimated. On the basis of this analysis of covariance, a two-sided test was carried out at the 5% significance level. A logistic regression model was used to evaluate the proportion of patients achieving BP goals. For all efficacy analyses, a last observation carried-forward approach was used to impute for missing values after baseline (baseline not carried forward).

## Results

### Patients

Patient disposition for the overall study population was reported earlier [13]. In brief, 728 patients were randomized (*n*=369, intensive treatment; *n*=359, moderate treatment). Of the 728 randomized patients, 280 naive patients were treated with a 20mg dose of olmesartan (*n*=146, intensive treatment; *n*=134, moderate treatment), 207 non-naive patients (who failed with any single agent other than an ARB) were treated with a 40 mg dose of olmesartan (*n*=103, intensive treatment; *n*=104, moderate treatment), and 241 non-naive patients (uncontrolled with ARB monotherapy) were directly randomized to the study drug (*n*=120, intensive treatment; *n*=121, moderate treatment). Seventy patients discontinued the study prematurely (*n*=33, *n*=37), primarily due to adverse events (*n*=9, *n*=19), withdrawal of consent (*n*=10, *n*=9), and protocol deviations (*n*=8, *n*=6).

Demographic and baseline characteristics for the 80 patients who comprised the ABPM substudy population (*n*=44, intensive treatment, *n*=36, moderate treatment) are shown in Table 1, and were generally similar to those of the overall study population. In the ABPM substudy population, no statistically significant between-group differences were observed. Overall, mean age was 54 years, and the majority of patients were female (53%) and Caucasian (54%). In this subset, at baseline, mean 24-h ASBP/ADBP was approximately 142/86mmHg, clinic SBP/DBP was 164/95mmHg, and home SBP/DBP was 162/93mmHg.

### Changes from baseline in 24-h mean ambulatory blood pressure

Mean ASBP (MASBP)/mean ADBP (MADBP) over 24 h was reduced from 140.7/87.4 mmHg at baseline to 125.7/77.2mmHg at week 4, the primary time point, with intensive treatment and from 143.5/85.3 to 133.4/ 79.4mmHg with moderate treatment (Table 2). The least-square mean difference between treatment groups was −6.71 (95% CI: −10.97 to −2.46)/ −3.66 (95% CI: −6.42 to −0.90)mmHg, in favor of a larger reduction with intensive treatment ($P$=0.0024/0.010; Fig. 2). Reductions from baseline to week 12 in both 24-h ASBP and ADBP were also significantly greater with intensive treatment ($P$<0.05 vs. moderate treatment). Findings for clinic and home BP in this subset of patients showed a trend in favor of intensive treatment at weeks 4 and 12; however, between-treatment comparisons did not achieve statistical significance except for clinic SBP at week 12 (Table 2; Fig. 2).

### Changes from baseline in daytime, night-time, and last 6-h ambulatory blood pressure

Results for MASBP and MADBP during the daytime, night-time, and last 6 h of the dosing interval consistently favored intensive treatment over moderate treatment, with the differences achieving statistical significance at week 4 for daytime, night-time, and last 6-h ASBP and at week 12 for daytime ASBP and ADBP measures (Table 3). Hourly ABPM data after 12 weeks of treatment are shown in Fig. 3.

### Blood pressure goal

Using ABPM measures, at week 4, a significantly greater proportion of patients receiving intensive treatment achieved the ABP goal (<130/80mmHg) than those receiving moderate treatment ($P$=0.040) (Fig. 4). There were no statistically significant differences between the intensive-treatment and moderate-treatment groups using the clinic or home BP goal (<140/90mmHg), although the findings generally favored intensive treatment (Fig. 4).

## Discussion

The objective of the primary study was to evaluate BP-lowering effects after initiation of intensive (10/320 mg) versus moderate (5/160 mg) amlodipine/valsartan treatment in mostly stage 2 hypertensive patients earlier uncontrolled on ARB monotherapy. Results from the overall study population were significant, in favor of the intensive treatment, in the lowering of clinic BP [13]. In this prespecified analysis, we evaluated the efficacy of an intensive versus a moderate treatment strategy using ABPM and compared the findings with clinic or home BP measures within the same subset of patients. This study is, to the best of our knowledge, the first in which all three methods of measuring BP (home, clinic, and 24-h ambulatory) were used to compare treatment effects using an intensive or moderate ARB regimen. Significant differences in treatment effects were observed using ABPM, whereas using clinic or home BP, treatment differences were not apparent. ABPM also identified treatment-group differences for change from baseline in daytime, night-time, and last 6-h ABP and for achievement of ABP goal.

Published trials on the efficacy of combination therapy with amlodipine and an ARB are limited, especially with respect to ABP. In a 12-month study, adding amlodipine to ARB treatment in a 50-patient cohort did not further reduce ABP or clinic BP, but did benefit measures of vascular function [9]. In a 12-week, open-label, prospective, single-arm, titrate-to-goal study [15,16], amlodipine/ olmesartan was uptitrated to a maximum of 10/40 mg in patients with stage 1 or 2 hypertension. In the 172 patients with available ABPM results, MASBP and MADBP decreased from baseline to week 12 by 21.4 mmHg and 12.7 mmHg, respectively (P<0.0001 for both comparisons) [15]; in the overall population, mean seated clinic SBP and DBP were reduced over the same time period by 24.6 mmHg and 12.3

mmHg, respectively ($P < 0.0001$ for both comparisons) [16]. Home BP was not reported for this study. Our findings using ABP are similar to the above, in that a decrease of 21.5 mmHg for SBP and of 13.7 mmHg for DBP was observed with the intensive arm.

In our ABPM substudy, baseline clinic SBP was approximately 20mmHg greater than daytime ASBP; this difference lessened at subsequent visits (approximately 9 to 13 mmHg difference). The greater difference between clinic and ABP observed at baseline in this study may have been due to white-coat effect, which diminished over time as patients became more familiar (and comfortable) with the clinic procedures [17]. Another interesting finding is that clinic BP was greater than home BP throughout the study, overall, by approximately 3.5/2.5 mmHg. Earlier studies have reported expected differences of 5–10/5 mmHg [18]. Use of the same BP device in the clinic and home settings, and proper instruction to patients and clinic staff on its use, may have contributed to the minimal differences between clinic and home BP measures.

In addition to eliminating white-coat hypertension, ABPM allows physicians to identify patients whose BP is increased at home (patients with ‘masked’ hypertension) and those whose BP does not decrease at night (‘nondippers’) or surges in the morning; these groups have been reported to be at higher risk for cardiovascular events [3,19–21]. In the Ohasama study, 1464 patients aged 40 years or older were followed for over 6 years. In that study, ABP was found to be a better predictor of stroke risk than clinic BP [22]. As noted in a recent American Society of Hypertension position statement, ABPM is considered the superior method for BP monitoring, particularly in evaluating antihypertensive effects of different drugs in the clinical trial setting [8]. The findings of this study support this contention and reinforce the use of ABPM in clinical trials to best identify treatment differences in BP lowering. However, our results in no way minimize the importance of home and office BP measures for making clinical decisions in actual practice. In fact, as stated in the American Society of Hypertension position article [8], these are the preferred methods in this setting, particularly given the impracticality of performing multiple ABPM sessions in the same patient.

## Study limitations

Limitations of the overall study, which have been reported earlier [13], include the absence of routine evaluation of laboratory parameters after initiation of study drug, preventing analysis of treatment effects on biochemical parameters throughout the study. In addition, it may have been useful to evaluate a titration schedule in which the maximum recommended doses were reached more slowly. Another potential limitation is the lack of an olmesartan dose increase during the run-in period. The treatment-naive patients received a 20mg dose of olmesartan once daily for 28 days before study drug initiation. As earlier studies have shown that the antihypertensive effect of a 20 mg dose plateaus within this time period and that olmesartan provides dose-related BP reduction over the range of 20 to 40 mg [23], patients may have benefited from doubling the olmesartan dose. A limitation of the ABPM analysis was its small sample size. In addition, to minimize any differences that timing might have on home versus office BP measures, a single home BP recording was done on the morning of each clinic visit rather than several times surrounding the time point of each ABPM measurement. This may have contributed to the lack of significant between-treatment findings with respect to home BP measurements.

## Conclusion

This is the first randomized trial that compared the effects of the combination of amlodipine/valsartan at intensive and moderate doses using three different BP measures: ambulatory, clinic, and home BP. Despite the small sample size of this substudy and the fact that home

BP was only measured as a single recording rather than multiple recordings, these data suggest that use of ABPM is better than clinic or home BP for comparison of the efficacy of various treatment strategies and further support the use of ABPM as the ‘gold standard’ for the evaluation of antihypertensive drugs.

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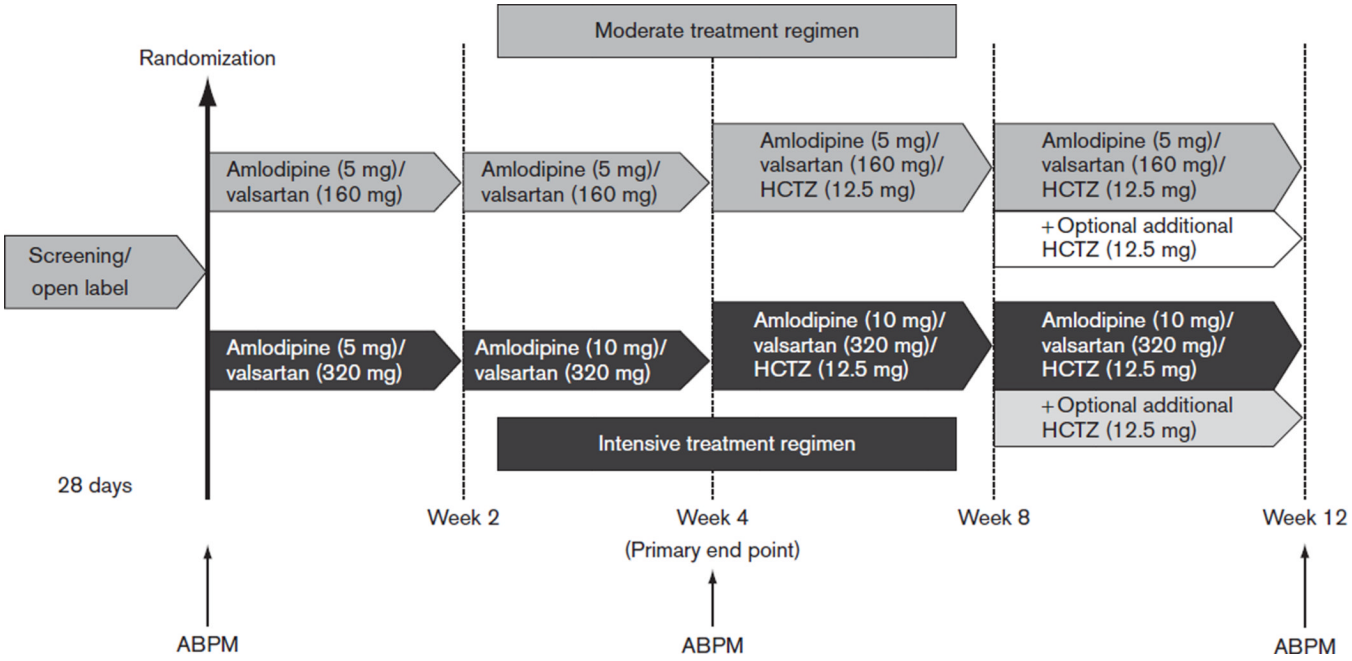


**Fig. 1.**
Study design. ABPM, ambulatory blood pressure monitoring; HCTZ, hydrochlorothiazide. Reproduced with permission from [13].

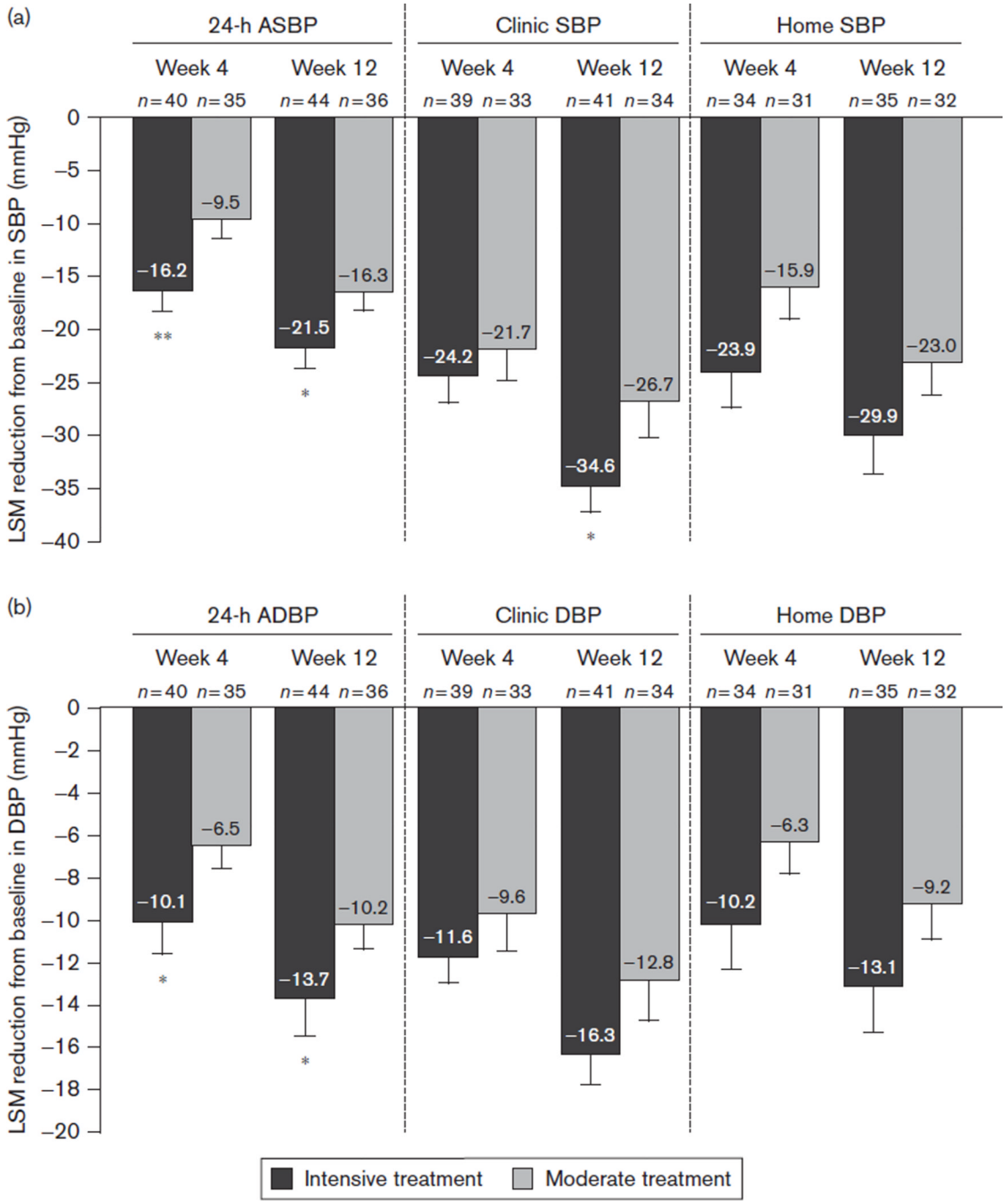


**Fig. 2.**

Least-square mean (LSM) reductions from baseline in 24-h ambulatory, clinic, and home systolic blood pressure (SBP, a) and diastolic blood pressure (DBP, b) during intensive treatment (amlodipine/valsartan =10/320 mg) versus moderate treatment (amlodipine/valsartan =5/160 mg) in the ambulatory blood pressure monitoring substudy population. Hydrochlorothiazide (12.5 mg) was added to both treatments at week 4, with optional additional hydrochlorothiazide 12.5mg at week 8. Error bars represent standard error. **P*<0.05; ***P*<0.01 vs. moderate treatment. ADBP, ambulatory diastolic blood pressure; ASBP, ambulatory systolic blood pressure.

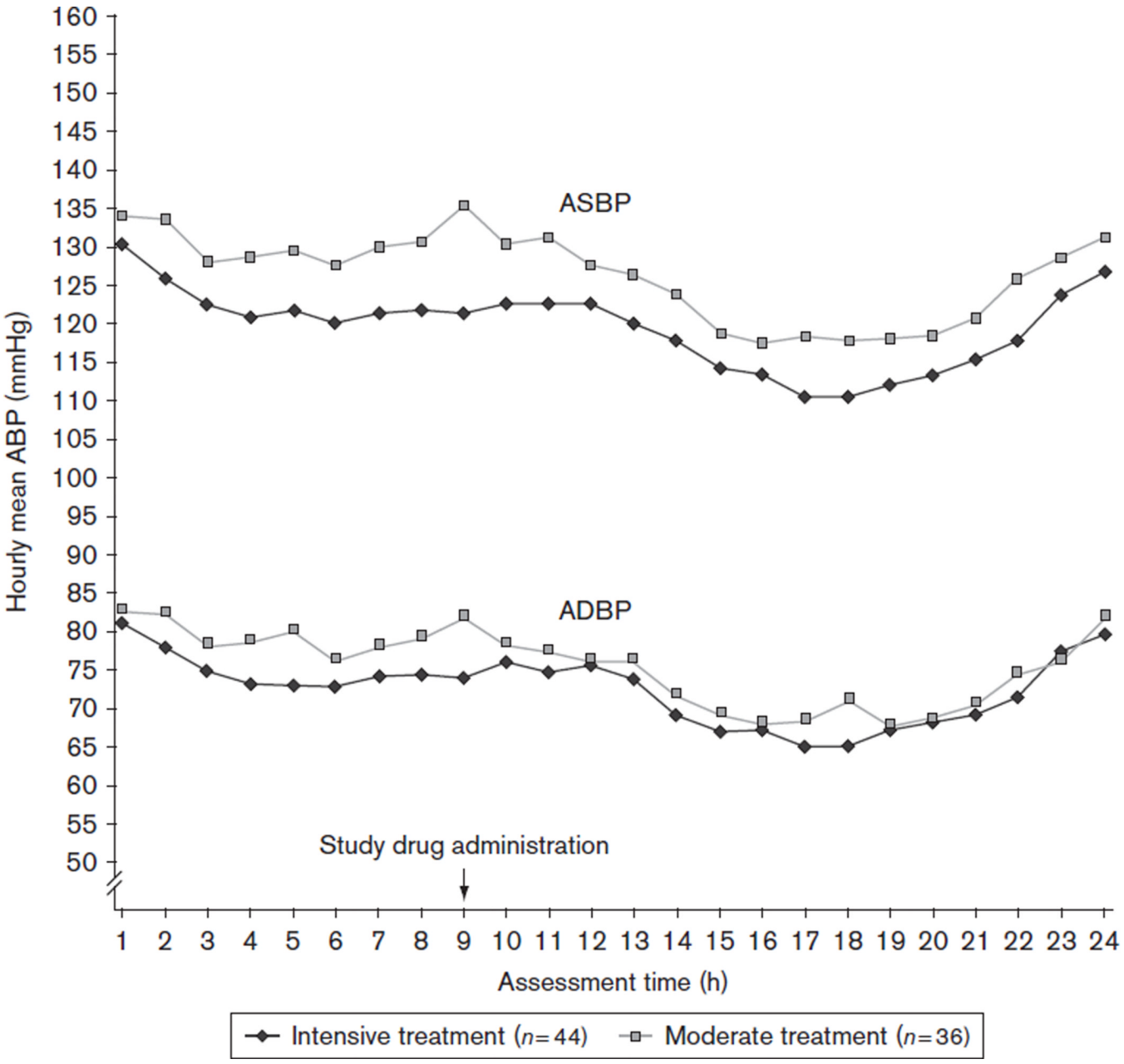


**Fig. 3.**

Hourly ambulatory systolic blood pressure (ASBP) and ambulatory diastolic blood pressure (ADBP) after 12 weeks of intensive treatment (amlodipine/valsartan =10/320 mg) versus moderate treatment (amlodipine/valsartan =5/160mg) in the ambulatory blood pressure (ABP) monitoring substudy population. The first dose hour starts at 09:00h. Hydrochlorothiazide (12.5 mg) was added to both treatments at week 4, with optional additional hydrochlorothiazide 12.5mg at week 8.

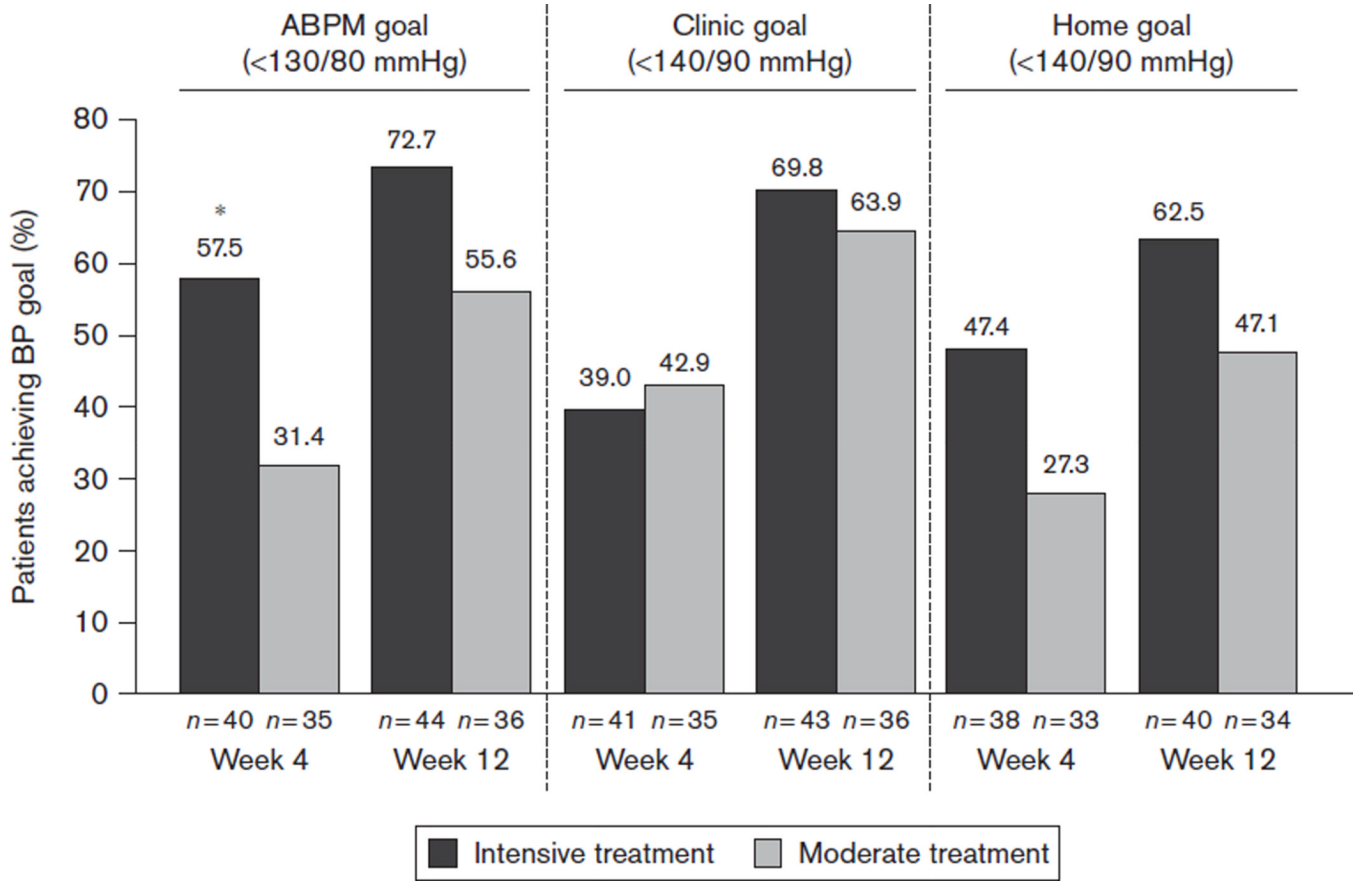


**Fig. 4.**

Proportion of patients achieving ambulatory, clinic, and home blood pressure (BP) goals during intensive treatment (amlodipine/valsartan = 10/ 320 mg) versus moderate treatment (amlodipine/valsartan= 5/160 mg) in the ambulatory blood pressure monitoring (ABPM) substudy population. Hydrochlorothiazide (HCTZ, 12.5 mg) was added to both treatments at week 4, with optional additional HCTZ 12.5 mg at week 8. By week 12, 127 (35%) patients in the intensive arm and 170 (48%) patients in the moderate arm were receiving 25 mg of HCTZ. This likely contributed to the lack of significant differences between the two treatment arms at week 12. P values are based on logistic regression. *$P$<0.05 vs. moderate treatment.

## Table 1

Demographic characteristics (ambulatory blood pressure monitoring substudy population)

| | **Intensive treatment (A/V=10/320 mg) (*n*=44)** | **Moderate treatment (A/V=5/160 mg) (*n*=36)** |
|---|---|---|
| Age (years) | 52.5 (10.1) | 56.5 (8.1) |
| *N* (%) ≥65 years | 3 (7) | 5 (14) |
| Sex [*N* (%)] | | |
| Male | 24 (55) | 14 (39) |
| Female | 20 (45) | 22 (61) |
| Race [*N* (%)] | | |
| Caucasian | 21 (48) | 22 (61) |
| African–American | 16 (36) | 10 (28) |
| Other | 7 (16) | 4 (11) |
| BMI ($kg/m^2$) | 28.8 (5.8) | 31.0 (6.9) |

Values are mean (standard deviation) unless otherwise noted.

A/V, amlodipine/valsartan.

**Table 2**

Week 4 BP changes as monitored by ambulatory, clinic, and home blood pressure measurements (ambulatory blood pressure monitoring substudy population)

| | Ambulatory BP | | Clinic BP | | Home BP | |
|---|---|---|---|---|---|---|
| | **Intensive treatment (A/V =10/320 mg)** | **Moderate treatment (A/V = 5/160mg)** | **Intensive treatment (A/V =10/320 mg)** | **Moderate treatment (A/V =5/160mg)** | **Intensive treatment (A/V = 10/320 mg)** | **Moderate treatment (A/V = 5/160mg)** |
| SBP (mmHg) | | | | | | |
| Baseline [mean (SD)] | 140.7 (15.4) *n*=44 | 143.5 (14.1) *n*=36 | 163.2 (10.7) *n*=42 | 165.7 (11.9) *n*=34 | 161.1 (15.8) *n*=36 | 162.0 (12.1) *n*=34 |
| Week 4 [mean (SD)] | 125.7 (10.4) *n*=4Q | 133.4 (13.0) *n*=35 | 140.8 (14.6) *n*=41 | 142.8 (15.9) *n*=35 | 138.3 (16.7) *n*=38 | 147.4 (16.8) *n*=33 |
| LSM Δ from baseline to week 4 | −16.21 | −9.50 | −24.21 | −21.65 | −23.93 | −15.92 |
| LSM difference (95% CI) | −6.71 (−10.97 to –2.46) | | −2.55 (−9.71 to 4.60) | | −8.01 (−16.14 to 0.1 2) | |
| *P* value | 0.0024 | | 0.48 | | 0.053 | |
| DBP (mmHg) | | | | | | |
| Baseline [mean (SD)] | 87.4 (1 2.8) *n*=44 | 85.3 (8.4) *n*=36 | 95.4 (10.7) *n*=42 | 93.7 (9.0) *n*=34 | 93.8 (12.3) *n*=36 | 91.7 (9.9) *n*=34 |
| Week 4 [mean (SD)] | 77.2 (8.7) *n*=40 | 79.4 (7.0) *n*=35 | 83.7 (11.1) *n*=41 | 84.7 (7.2) *n*=35 | 82.8 (11.3) *n*=38 | 85.9 (8.8) *n*=33 |
| LSM Δ from baseline to week 4 | −10.13 | −6.48 | −11.61 | −9.58 | −10.24 | −6.32 |
| LSM difference (95% CI) | −3.66 (−6.42 to –0.90) | | −2.03 (−6.05 to 2.00) | | −3.92 (−8.44 to 0.60) | |
| *P* value | 0.010 | | 0.32 | | 0.088 | |

A/V, amlodipine/valsartan; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; LSM, least-square mean; LSM Δ, least-square mean change; SBP, systolic blood pressure; SD, standard deviation.

## Table 3

Daytime, night-time, and last 6-h ambulatory blood pressure findings (ambulatory blood pressure monitoring substudy population)

| | Intensive treatment (A/V =10/320 mg) | Moderate treatment (A/V =5/160 mg) |
|---|---|---|
| Daytime (06:00 h–22:00 h) ASBP/ADBP (mmHg) | | |
| Baseline [mean (SD)] | 143.9 (14.8)/90.3 (12.5) *n*=44 | 146.5 (14.1)/88.4 (8.5) *n*=36 |
| Week 4 [mean (SD)] | 129.2 (10.5)/80.3 (9.1) *n*=40 | 136.6 (13.3)/82.4 (7.4) *n*=35 |
| LSM Δ from baseline to week 4 | − 15.92**/ − 10.07* | − 9.40/ −6.50 |
| Week 12 [mean (SD)] | 122.8 (11.9)/75.7 (9.0) *n*=44 | 130.1 (13.2)/78.8 (7.6) *n*=36 |
| LSM Δ from baseline to week 12 | −21.85*/ − 14.12* | − 15.59/ − 10.19 |
| Night-time (22:00 h–06:00 h) ASBP/ADBP (mmHg) | | |
| Baseline [mean (SD)] | 134.7 (18.0)/81.8 (14.5) *n*=44 | 137.6 (16.7)/79.4 (9.6) *n*=36 |
| Week 4 [mean (SD)] | 118.9 (12.2)/71.2 (9.6) *n*=40 | 127.4 (14.6)/73.7 (8.0) *n*=35 |
| LSM Δ from baseline to week 4 | − 16.91**/ −10.36* | −9.45/ −6.60 |
| Week 12 [mean (SD)] | 114.6 (13.5)/68.1 (9.2) *n*=44 | 119.0 (11.7)/69.6 (6.8) *n*=36 |
| LSM Δ from baseline to week 12 | −20.93/ −13.07 | − 17.66/−10.67 |
| Last 6-h ASBP/ADBP (mmHg) | | |
| Baseline [mean (SD)] | 137.2 (15.1)/85.2 (12.7) *n*=44 | 141.9 (15.1)/84.2 (9.9) *n*=36 |
| Week 4 [mean (SD)] | 123.9 (12.6)/76.3 (10.9) *n*=40 | 131.3 (13.9)/78.3 (8.8) *n*=35 |
| LSM Δ from baseline to week 4 | − 14.63*/ − 8.99 | − 8.83/ − 5.88 |
| Week 12 [mean (SD)] | 119.1 (13.2)/73.1 (10.2) *n*=44 | 123.3 (12.5)/73.2 (8.2) *n*=36 |
| LSM Δ from baseline to week 12 | − 19.42/ − 11.82 | − 16.99/ − 11.28 |

A/V, amlodipine/valsartan; ADBP, ambulatory diastolic blood pressure; ASBP, ambulatory systolic blood pressure; LSM Δ, least-square mean change; SD, standard deviation.

* *P*<0.05 vs. moderate treatment.

** *P*<0.01 vs. moderate treatment.