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Moderate versus intensive treatment of hypertension with amlodipine/valsartan for patients uncontrolled on angiotensin receptor blocker monotherapy

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Abstract

Objectives—Many angiotensin receptor blocker (ARB) monotherapy patients need at least two agents to control blood pressure (BP). We investigated whether initiating intensive treatment with combination amlodipine/valsartan was superior to moderate treatment with amlodipine/valsartan in patients previously uncontrolled on ARB monotherapy.

Methods—In this 12-week study, patients aged at least 18 years on ARB (other than valsartan) for at least 28 days (with treatment-naïve patients or those not controlled on agents other than an ARB treated with open-label olmesartan 20 or 40 mg, respectively, for 28 days) and with uncontrolled mean sitting systolic blood pressure (MSSBP; ≥150–<200 mmHg) were randomized to amlodipine/valsartan 5/320 mg (n = 369) or 5/160 mg (n = 359). At week 2, the dose was increased to 10/320 mg in the intensive arm. Hydrochlorothiazide 12.5 mg was added to both arms at week 4. Optional up-titration with hydrochlorothiazide 12.5 mg at week 8 was allowed if MSSBP was more than 140 mmHg.

Results—At baseline, mean office sitting BP was comparable in the intensive (163.9/95.5 mmHg) and moderate (163.3/95.0 mmHg) groups. Intensive treatment provided greater BP reductions versus moderate treatment (P<0.05) from week 4 (−23.0/−10.4 versus −19.2/−8.7 mmHg; primary endpoint) to week 12 (−29.0/−14.8 versus −25.3/−12.3 mmHg). Adverse events were reported by a similar percentage of patients in both groups (36.3% intensive, 37.6% moderate); peripheral edema was more common with intensive versus moderate treatment (8.7 versus 4.5%; P=0.025).

Conclusions—Initiating treatment with an intensive dose of amlodipine/valsartan provides significantly greater BP lowering versus moderate treatment in hypertensive patients unresponsive to ARB monotherapy. Both treatment regimens were generally well tolerated based on adverse event reports, but the lack of routine laboratory testing after screening limits conclusions on tolerability.

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Keywords

amlodipine; blood pressure; efficacy; hydrochlorothiazide; hypertension; safety; valsartan

Introduction

Hypertension is associated with an increased risk for adverse cardiovascular, cerebrovascular, and renal events [1,2]. Moreover, in a meta-analysis of 61 studies involving approximately 1 million patients, blood pressure (BP) was strongly related to the risk of death from cardiovascular causes down to a BP of 115/75 mmHg [3]. Among individuals 40–69 years of age, each systolic BP (SBP) difference of 20 mmHg or diastolic BP (DBP) difference of 10 mmHg was associated with a more than two-fold difference in the death rate from stroke and with two-fold differences in the death rates from ischemic heart disease and other vascular causes [3]. In the 50 years since the introduction of thiazide diuretics, numerous studies have shown the clear-cut benefits of antihypertensive therapy [2,4]. However, despite the availability of several classes of antihypertensive agents and several agents in each class from which to choose, achieving target BP (<140/90 mmHg or <130/80 mmHg in higher-risk patients [5,6]) is difficult in many patients. In the US, improvements in hypertension awareness and treatment have resulted in improvements in BP control over the past decade, although nearly half of all hypertensive adults still have BP that is inadequately controlled [7].

Current hypertension guidelines acknowledge that combination therapy is necessary for most patients to attain recommended BP targets and, in some cases, should be considered as first-line therapy [5,6,8]. Specifically, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends starting patients with combination therapy when BP is greater than 20/10 mmHg above goal [5]. European guidelines recommend combination therapy as a first step when initial BP is at least 160/100 mmHg or when cardiovascular risk is high (e.g. presence of diabetes, the metabolic syndrome, or renal disease) [6,8]. In line with these recommendations, the US Food and Drug Administration recently approved several single-pill combinations [e.g. thiazide diuretic and angiotensin receptor blocker (ARB) or direct renin inhibitor (DRI); dihydropyridine calcium channel blocker (DHP-CCB) and ARB] as initial therapy in patients likely to require multiple drugs to achieve BP goals.

Combining a DHP-CCB with a RAAS inhibitor [angiotensin-converting enzyme inhibitor (ACEI), ARB, or DRI] is a rational approach for combination antihypertensive therapy [9] and is advocated in treatment guidelines [6,8,10]. These drug classes have complementary mechanisms of action, providing greater BP reduction than treatment with component monotherapy [11–13]; in addition, they have ancillary effects that may further contribute to their vascular benefits (e.g. improve nitric oxide bioavailability, reduce oxidative stress, suppress inflammation) [9]. In the recent Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study, first-line therapywithaDHP-CCB/ACEIcombination (amlodipine/benazepril) conferred greater reduction in cardiovascular morbidity and mortality rates than did a thiazide diuretic/ ACEIcombination[hydrochlorothiazide(HCTZ)/benazepril] in high-risk hypertensive patients [14]. From a tolerability perspective, ACEIs and ARBs can lessen the occurrence of peripheral edema commonly associated with DHP-CCBs [15,16].

For patients who are appropriate candidates for DHP-CCB/ARB therapy, an important challenge for clinicians is to determine the optimal doses at which to start treatment. In the current study, we investigated whether initiating an intensive-treatment strategy with the

DHP-CCB/ARB combination of amlodipine/valsartan was superior to a moderate-treatment strategy with the same combination in patients with systolic hypertension previously uncontrolled with ARB monotherapy.

Methods

Patients

Exforge target achievement (EXTRA) study was conducted in men and women at least 18 years of age who were treatment-naïve or whose BP was uncontrolled with previous monotherapy and with a documented diagnosis of systolic hypertension [mean sitting SBP (MSSBP) ≥150 mmHg and <200 mmHg]. Key exclusion criteria included a history of notable cerebrovascular or cardiovascular disease within 6 months before the screening visit; abnormal serum electrolyte levels at screening (sodium <135 mEq/l; potassium <3.5 or >5.5 mEq/l); evidence of hepatic disease (determined by any of the following: aspartate aminotransferase or alanine aminotransferase values greater than twice the upper limit of normal, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt); chronic kidney disease {determined by any of the following: a history of dialysis or a history of nephrotic syndrome and estimated glomerular filtration rate <50 ml/min per 1.73 m^2 [Modification of Diet in Renal Disease (MDRD) method] in the 3 months before screening}, pancreatic disease, or injury; and uncontrolled, treated type 2 diabetes (glycosylated hemoglobin >8.5%). Women who were pregnant, breast-feeding, or of child-bearing potential and not using an acceptable method of contraception were also excluded.

Ethics committee and/or institutional review board approval was granted at all participating centers, and all patients gave written informed consent before enrollment. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki.

Study design

The multicenter, randomized, double-blind, parallel-group study was conducted at 140 centers in the US. Patients previously uncontrolled on ARB monotherapy (other than valsartan) after at least 28 days (MSSBP ≥150 mmHg and <200 mmHg) were randomized directly to double-blind treatment. Patients who were naïve to antihypertensive therapy within the previous 28 days entered the open-label run-in phase, during which they received olmesartan 20 mg for 28 days. Patients who failed on any single agent other than an ARB also entered the open-label run-in phase, during which they received olmesartan 40 mg for 28 days. Thereafter, olmesartantreated patients (20 or 40 mg) whose BP remained uncontrolled and who satisfied the other inclusion/exclusion criteria were randomized to double-blind treatment.

Eligible patients were randomized (1 : 1) to either intensive or moderate treatment with single-pill combination amlodipine/valsartan (Fig. 1). Patients in the intensive group received a 5/320-mg dose, and those in the moderate group received a 5/160-mg dose for 2 weeks. At week 2, the dose in the intensive group was increased to 10/320 mg, and patients in the moderate group continued with the same dose of 5/160 mg. HCTZ was added for all patients at week 4 (12.5 mg) and optionally up-titrated at the discretion of the physician at week 8 (to a maximum dose of 25 mg) in patients whose SBP was not controlled (MSSBP >140 mmHg). Down-titration to the previous dose level was permitted, at the investigator's discretion, if patients experienced peripheral edema or signs/symptoms of hypotension. Patients were withdrawn from the study if MSSBP was greater than 200 mmHg and/or if mean sitting DBP (MSDBP) was at least 120 mmHg.

Concomitant medications likely to interfere with evaluation of the study medication, including any nonstudy antihypertensive agent, were prohibited throughout the trial.

Sildenafil and vardenafil were disallowed within 24 h and tadalafil was disallowed within 48 h before any scheduled visit.

Blood pressure assessments and adverse events

Office BP measurements were made using an automated BP monitor (Model #HEM-705CP; Omron, Schaumburg, Illinois, USA) in accordance with the guidelines of the British Hypertension Society [17]. Sitting BP was measured at each visit. Patients rested for a minimum of 5 min before any measurements were taken. Three replicate BP measurements were obtained at least 2 min apart, and the mean of these three measurements was used as the average sitting BP. The primary efficacy outcome was the change from baseline to week 4 in MSSBP. Secondary efficacy outcomes included the change from baseline to weeks 2, 8, and 12 in MSSBP, the change from baseline to all time points in MSDBP, the proportion of patients achieving the overall BP goal (<140/90 mmHg), and the proportion of patients achieving the MSSBP goal (<140 mmHg).

Safety was assessed in all randomized patients who received at least one dose of the double-blind study drug. Safety assessments consisted of recording all adverse events and serious adverse events, with severity and relationship to study drug; measurement of vital signs; performance of physical examinations; and evaluation of hematology, blood chemistry, and urine levels at a central laboratory (screening only).

Prespecified exploratory outcomes

Prespecified exploratory outcomes analyzed for this study included the change from baseline in MSSBP and MSDBP in patients with severe hypertension (baseline MSSBP >180 mmHg) and elderly patients (≥65 years of age). In addition, analyses were performed based on sex and race. The proportion of diabetic patients achieving BP goal, which was prespecified to be below 130/80 mmHg, was also determined.

Statistical methods

A sample size of 678 patients (339 per treatment regimen) was necessary to ensure 85% power to detect a difference in reduction of at least 3 mmHg in MSSBP and to conclude the superiority of intensive treatment over moderate treatment in the primary efficacy outcome. All randomized patients who received at least one dose of study drug and who had at least one postbaseline assessment of the primary efficacy outcome were included. A last observation carried forward (LOCF) approach was used to impute for missing values postbaseline. Within-treatment changes from baseline were analyzed using a paired *t* test and between-treatment differences using an analysis of covariance (ANCOVA) model with baseline MSSBP, treatment, and olmesartan dosage in run-in phase and substudy-based stratum (whether or not a patient participated in the ambulatory BP monitoring substudy, augmentation index monitoring substudy, or neither substudy) as explanatory variables. 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-squared means of each treatment arm were also computed. On the basis of this ANCOVA analysis, a two-sided test was performed at the 5% significance level. The intensive regimen was considered superior to the moderate regimen if the null hypothesis of no difference was rejected and a larger change from baseline was detected for the intensive regimen. All other BP changes (i.e. MSDBP and subgroup analyses) were analyzed similarly. For testing of differences in the proportion of patients achieving BP goals (LOCF), *P* values were based on logistic regression. Demographic and baseline characteristics were analyzed using a two-sample *t* test, chi-squared test, or Fisher's exact test. Treatment groups were compared with respect to the incidence of peripheral edema and discontinuations due to adverse events using Fisher's exact test or chi-squared test.

Results

Patients

Of the 1589 patients who were screened, 660 did not meet study entry criteria at the screening visit and 201 did not complete the olmesartan run-in phase [BP was controlled or they did not satisfy the other inclusion/exclusion criteria (n =151), withdrew consent (n=16), adverse events (n=11), lost to follow-up (n=7), protocol deviations (n=7), and other (n=9)]. Therefore, 728 patients were randomized (369 intensive treatment, 359 moderate treatment). Disposition for randomized patients is shown in Fig. 2.

Overall, mean age at baseline was approximately 55 years (18% ≥65 years), 57% were men, 27% were black, and 16% were diabetic (see definition in Table 1). The mean serum creatinine level was 0.90 mg/dl, and mean estimated glomerular filtration rate (MDRD method) was 92.2 ml/min per 1.73 m^2. The study population was predominantly obese, with a mean body mass index of 32 kg/m^2. Mean office sitting BP was 163.6/95.3 mmHg. The only significant difference (P<0.05) between the two treatment groups was mean waist circumference, which was slightly greater in the moderate-treatment arm (103.4 cm) than in the intensive-treatment arm (100.9 cm). Demographic and baseline characteristics are shown by treatment group in Table 1. The maximum doses of study medication were received by 35% of patients in the intensive-treatment group (amlodipine/valsartan/HCTZ 10/320/25 mg) and 48% in the moderate-treatment group (amlodipine/valsartan/HCTZ 5/160/25 mg) (P<0.001).

Changes in MSSBP and MSDBP from baseline

Both treatments produced significant reductions from baseline to all time points in MSSBP and MSDBP (all P<0.0001). For the primary efficacy outcome, MSSBP was reduced from 163.9 mmHg at baseline to 140.9 mmHg at week 4 with intensive treatment and from 163.3 to 144.4 mmHg with moderate treatment (Fig. 3). The least-square mean difference between treatment groups was −3.81 mmHg (95% CI −5.73 to −1.89; P=0.0001) in favor of a larger reduction with intensive treatment. MSDBP was reduced from 95.5 mmHg at baseline to 84.8 mmHg at week 4 with intensive treatment and from 95.0 to 86.2 mmHg with moderate treatment. The least-square mean difference between treatment groups was −1.74 mmHg (95% CI −2.95 to −0.54; P=0.0047) in favor of a larger reduction with intensive treatment. As shown in Fig. 3, reductions from baseline to weeks 8 and 12 in both MSSBP and MSDBP were also significantly greater with intensive treatment (all P<0.001).

Blood pressure goal

At weeks 4, 8, and 12, a significantly greater proportion of patients receiving intensive treatment achieved BP goal (<140/90 mmHg) than those receiving moderate treatment (all P<0.01) (Fig. 4). The proportion of patients achieving the MSSBP goal (<140 mmHg) at weeks 4, 8, and 12 in the intensive-treatment arm were 49.2, 66.1, and 62.8%, respectively; corresponding results with moderate treatment were 37.5, 49.6, and 55.7% (P<0.05 for comparisons between groups at all time points). No significant differences were observed between the two treatment groups at week 2.

Prespecified subgroup analyses

Mean sitting systolic blood pressure reductions in the 73 patients with severe hypertension (baseline MSSBP >180 mmHg) were robust and numerically or significantly greater with intensive treatment than with moderate treatment (Fig. 5). Antihypertensive efficacy was maintained in the 129 elderly patients (Fig. 6) and 198 black individuals (data not shown). In women (n=314), intensive treatment reduced MSSBP/MSDBP from 164.8/93.9 mmHg at baseline to 133.7/79.5 mmHg at week 12, whereas moderate treatment reduced MSSBP/

MSDBP from 163.3/93.5 to 137.0/82.4 mmHg ($P<0.05$/$P<0.01$ between treatments). In the diabetic subgroup ($n=118$ or 16% of total population), the proportion of patients who achieved BP less than 130/80 mmHg at weeks 4 and 12 was numerically greater with intensive treatment (18.9 and 32.1%, respectively) than with moderate treatment (7.7 and 20.0%, respectively).

Adverse events

Adverse events were experienced by 134 patients (36.3%) in the intensive-treatment group and by 135 patients (37.6%) in the moderate-treatment group. Adverse events were generally reported at a low and similar frequency in the two treatment groups (Table 2). The most frequent adverse event was peripheral edema, which was nearly twice as common with intensive treatment (8.7%) as with moderate treatment (4.5%) ($P=0.025$). Most cases of peripheral edema were mild [only one case of severe intensity (moderate-treatment group)]. Dizziness and hypotension were reported as adverse events in 5.1 and 1.1% of patients, respectively, during intensive treatment and in 3.9 and 0.8% during moderate treatment. Among patients who received the maximum allowed doses of study medication (35% in intensive arm, 48% in moderate arm), adverse event rates were 11.8 versus 12.9% before week 2, 23.6 versus 22.4% before week 4, 33.1 versus 28.8% before week 8, and 40.2 versus 37.6% before week 12. These rates were similar to those of the overall population.

The occurrence of adverse events led to study discontinuation for 9 patients (2.4%) in the intensive-treatment group and 19 patients (5.3%) in the moderate-treatment group, a difference that was not statistically significant ($P=0.62$); the only adverse events to result in discontinuation for more than one patient was peripheral edema ($n=2$) in the intensive-treatment group and dizziness, headache, hypertension, myocardial infarction, and peripheral edema (each $n=2$) in the moderate-treatment group. Dizziness and hypotension each led to the discontinuation of one patient in the intensive-treatment group. No deaths occurred during the study.

Hyperkalemia was reported as an adverse event in a 74-year-old Caucasian man in the intensive-treatment group. The patient was receiving amlodipine/valsartan 10/320 mg when, on day 71, he was diagnosed with moderate hyperkalemia (6.1 mEq/l) and renal failure (blood urea nitrogen, 39 mg/dl; serum creatinine, 1.56 mg/dl). (At screening, the patient had potassium and blood urea nitrogen levels of 4.9 mEq/l and 18 mg/dl, respectively, and a serum creatinine level of 1.31 mg/dl, which was above the normal range of 0.7–1.2 mg/dl.) The patient continued treatment for another 2 days and was then discontinued from the study because of these adverse events. Both adverse events (hyperkalemia and renal failure) were ongoing at the time of the patient's last study visit. Hypokalemia was reported as an adverse event by one patient in the moderate-treatment group. The event was not serious and did not result in patient discontinuation. There were no specific adverse event reports of abnormal serum creatinine values.

Discussion

The results of this study show that, in patients with documented systolic hypertension whose BP was uncontrolled with ARB monotherapy, intensive treatment with the combination of amlodipine/valsartan [with titration up to the maximal recommended doses of amlodipine/valsartan/HCTZ (10/320/25 mg)] produced a greater antihypertensive effect than moderate treatment with the same agents. At weeks 4, 8, and 12, intensive treatment was significantly more effective than moderate treatment in reducing MSSBP/MSDBP, with differences ranging from approximately 4–5/2–3 mmHg. In addition, approximately 10–25% more patients on intensive treatment reached their BP goal (<140/90 mmHg) or MSSBP goal (<140 mmHg) over the course of the study.

Combination therapy is recommended for patients whose BP does not respond adequately to monotherapy and as initial treatment for patients with stage 2 hypertension or high cardiovascular risk [5,6,8]. The use of drugs with complementary mechanisms of action, such as a DHP-CCB and ARB, can help address the multifactorial nature of hypertension [18] and allow patients to reach BP targets more promptly [19], which may have important clinical implications [20]. Patients randomized in our study did not respond to ARB monotherapy, and the majority had stage 2 hypertension (mean baseline MSSBP of 163.6 mmHg). Our findings are consistent with those of other studies in which amlodipine/valsartan or other DHP-CCB/ARB combinations (e.g. amlodipine/olmesartan) were administered to hypertensive patients in whom a monotherapy approach was ineffective and/or who had stage 2 hypertension [21–29]. Amlodipine/valsartan has previously shown clinically meaningful BP reduction in difficult-to-treat patients (e.g. black, obese, elderly, or diabetic individuals, and those with severe hypertension) regardless of previous antihypertensive therapy [21,22,24,27,30]. Our prespecified subgroup analyses provide some support for initiating a more intensive treatment strategy in many of these populations, but were not powered to allow definitive conclusions.

Calhoun *et al.* [25] conducted an 8-week, randomized, double-blind study in 2271 patients with stage 2 hypertension that included a triple therapy arm (amlodipine/valsartan/HCTZ forced titrated up to 10/320/25 mg) and three dual therapy arms (amlodipine/valsartan, amlodipine/HCTZ, and valsartan/HCTZ). At study end, BP control (<140/90 mmHg) was achieved by 71% of patients on triple therapy compared with 45–54% on the dual therapies (all $P<0.0001$). In comparison, a lower proportion of patients (60%) in our study attained the same BP goal. The more favorable results observed by Calhoun *et al.* may be related to several factors. For example, their study enrolled a slightly younger population (14 versus 18% were ≥65 years) and a lower proportion of black individuals (17 versus 27%). In addition, our study design called for HCTZ 12.5 mg to be an add-on therapy for all patients at week 4. Thereafter, investigators had the option to up-titrate the dose of HCTZ to 25 mg at week 8, such that 35% of patients in the intensive-treatment group received the maximum recommended doses of all three study drugs (i.e. amlodipine/valsartan/HCTZ 10/320/25 mg). Thus, the majority of patients in this treatment arm (65%) never received the maximum dose of all three agents, and those who did were only treated for 4 weeks. In contrast, patients randomized to triple therapy in the study by Calhoun *et al.* were all force-titrated to maximum dose, and this treatment was administered for 6 weeks. Nonetheless, both studies showed robust reductions in BP with the maximum recommended doses of amlodipine, valsartan, and HCTZ.

Clinically meaningful BP reductions have also been observed during a 16-week double-blind phase followed by a 28-week, open-label, stepped-care extension, in which 27 patients needed the maximum recommended doses of amlodipine/olmesartan/HCTZ (10/40/25 mg) [28]. In this subgroup, which included patients unable to achieve BP less than 140/90 mmHg at previous up-titration steps and, therefore, more difficult to treat, MSSBP/MSDBP was reduced from baseline to study end by 17.5/10.8 mmHg.

Concerns among clinicians regarding the tolerability of an intensive-treatment approach may limit its use in clinical practice. Laboratory assessments were performed at screening only, which limits our conclusions on tolerability. However, based on adverse event reporting, both the intensive and moderate-treatment regimens used in our study were generally well tolerated. As expected, peripheral edema, a dose-related side effect of amlodipine therapy [31], occurred significantly more frequently in the intensive-treatment arm (8.7%) than in the moderate-treatment arm (4.5%), but most cases were mild and only four (2/group) resulted in study discontinuation. There is some evidence that the use of an ARB can minimize the occurrence of peripheral edema associated with DHP-CCB therapy. For

example, in a previous study, a more than four-fold lower incidence of peripheral edema was reported in hypertensive patients treated with amlodipine/valsartan than with amlodipine alone [16]. In addition, more than half the patients who experienced peripheral edema with amlodipine monotherapy experienced resolution of the event when switched to amlodipine/valsartan combination therapy [16]. In the current study, dizziness and hypotension were more common with intensive treatment (5.1 and 3.9%, respectively) than with moderate treatment (1.1 and 0.8%, respectively), but rarely were treatment limiting. There was one case of renal failure reported in a patient receiving amlodipine/valsartan 10/320 mg. In the study by Calhoun *et al.* the incidences of peripheral edema, dizziness, and hypotension during triple therapy with amlodipine/valsartan/HCTZ 10/320/25 mg were 4.5, 7.7, and less than 2%, respectively, with corresponding low rates of discontinuation owing to these events (0.2, 1.0, and 0.7%) [25]. No significant metabolic abnormalities or reports of deterioration in renal function were found. In the aforementioned open-label study, the only adverse event to be reported among amlodipine/olmesartan/HCTZ 10/40/25 mg recipients was one case of elevated blood uric acid level [28].

Study limitations

As mentioned above, a limitation of our study design was that laboratory parameters were not routinely evaluated after initiation of study medication; therefore, changes from the screening visit could not be analyzed. In addition, it might have been useful to assess a titration schedule in which the maximum recommended doses were reached more slowly over time. For example, patients could have begun treatment with amlodipine/valsartan 5/160 mg with subsequent up-titration to 5/320 mg and then 10/320 mg followed by the addition of HCTZ. This may have lowered the incidence of peripheral edema and hypotension-related adverse events, compared with the more intensive treatment approach used herein.

Patients who were naïve to antihypertensive therapy within the 28 days before screening, and who met the study entry criteria, participated in a run-in period during which they received olmesartan 20 mg once daily for 28 days. Previous findings have shown that the antihypertensive effect of a 20-mg dose plateaus within this time period, with minimal additional effectiveness during continued administration [23]. In our study, after receiving treatment with olmesartan 20 mg, eligible patients were then directly randomized without dose escalation to olmesartan 40 mg. However, because olmesartan seems to provide dose-related BP reduction over the 20–40-mg range [23], patients may have benefitted from doubling of the dose.

Our study was not designed to test for effects on clinical outcomes, and no such data are available on the combination of amlodipine/valsartan. However, amlodipine and valsartan-based therapy [32–35], including combination amlodipine/ACEI therapy [14,33], have shown benefits on cardiovascular morbidity and mortality rates in land-mark studies of hypertensive patients. The intensive treatment approach used herein provided more prompt BP reduction and control relative to moderate treatment, which has the potential to translate into improved clinical outcomes. For example, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, regardless of assigned treatment, clinical outcome benefits were significantly greater in ‘immediate’ versus ‘nonimmediate’ responders [36]. ‘Immediate’ responders were defined as previously treated patients who did not have a SBP increase when switched to study drug or previously untreated patients with an initial SBP decrease of at least 10 mmHg within the first month.

In conclusion, in patients with systolic hypertension (predominantly stage 2) whose BP is uncontrolled with ARB monotherapy, starting an intensive-treatment strategy with amlodipine/valsartan, with titration up to maximum recommended doses of amlodipine/

valsartan/HCTZ (10/320/25 mg), provides significantly greater antihypertensive effectiveness than a moderate-treatment strategy with the same agents. Both the intensive and the moderate-treatment regimens were generally well tolerated based on adverse event reports, but the lack of routine laboratory testing after screening limits our conclusions on tolerability.

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Abbreviations

ACCOMPLISH	Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
BMI	body mass index
CCB	calcium channel blocker
CI	confidence interval
eGFR	estimated glomerular filtration rate
EXTRA	Exforge target achievement study
HCTZ	hydrochlorothiazide
LOCF	last observation carried forward
MDRD	modification of diet in renal disease
MSDBP	mean sitting diastolic blood pressure

MSSBP	mean sitting systolic blood pressure
RAAS	renin-angiotensin-aldosterone system

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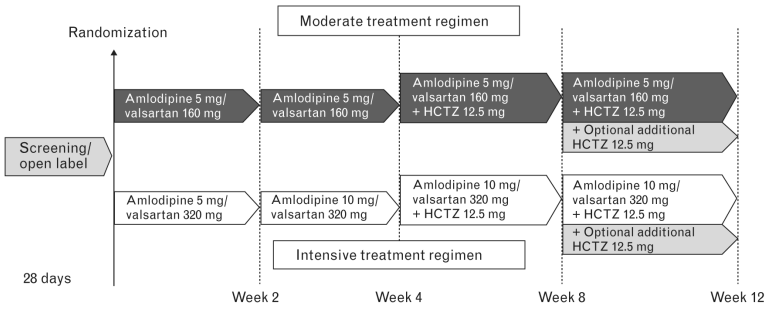

Fig. 1.
Study design. HCTZ, hydrochlorothiazide.

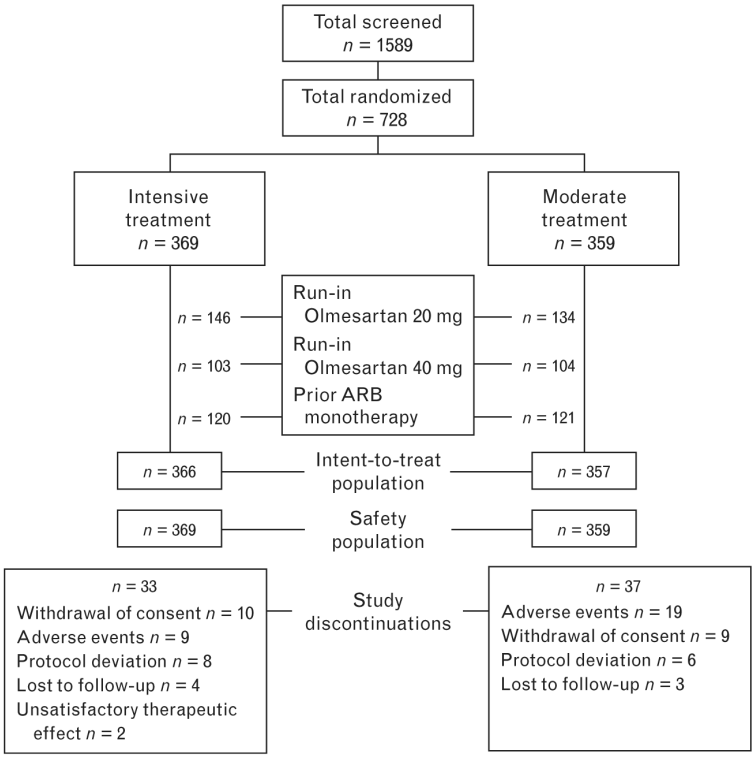

Fig. 2.
Patient disposition.

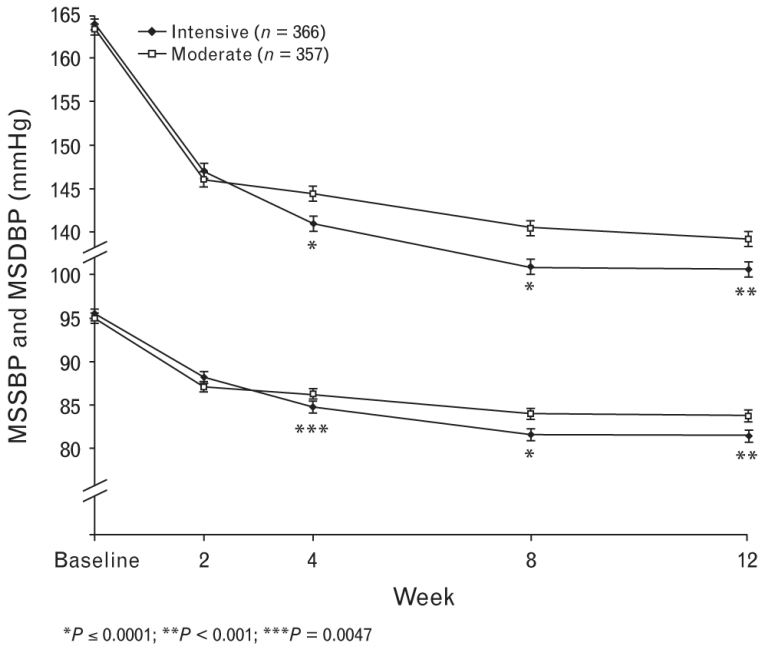

Fig. 3.

Mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) during double-blind treatment with intensive treatment (single-pill amlodipine 10 mg/valsartan 320 mg) versus moderate treatment (single-pill amlodipine 5 mg/valsartan 160 mg). Hydrochlorothiazide (HCTZ) 12.5mg was added to both treatments at week 4, with optional additional HCTZ 12.5mg at week 8. Error bars represent standard error.

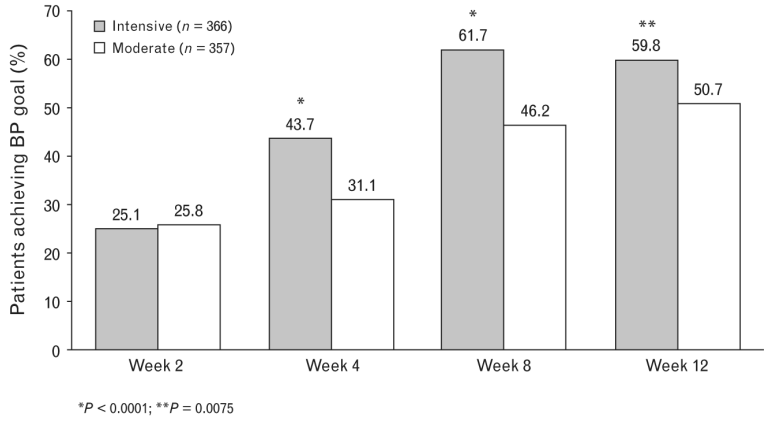

Fig. 4.

Proportion of patients achieving blood pressure goal (<140/90mmHg) during double-blind treatment with intensive treatment (single-pill amlodipine 10 mg/valsartan 320 mg) versus moderate treatment (single-pill amlodipine 5 mg/valsartan 160 mg). Hydrochlorothiazide (HCTZ) 12.5mg was added to both treatments at week 4, with optional additional HCTZ 12.5mg at week 8. *P* values are based on logistic regression.

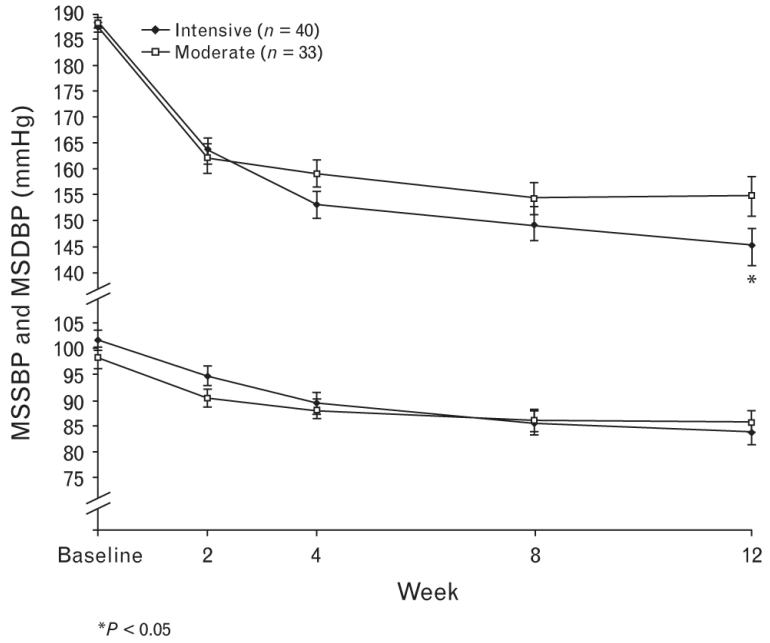

Fig. 5.

Mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) among patients with severe hypertension (baseline MSSBP ≥180mmHg) participating in the study. Error bars represent standard error.

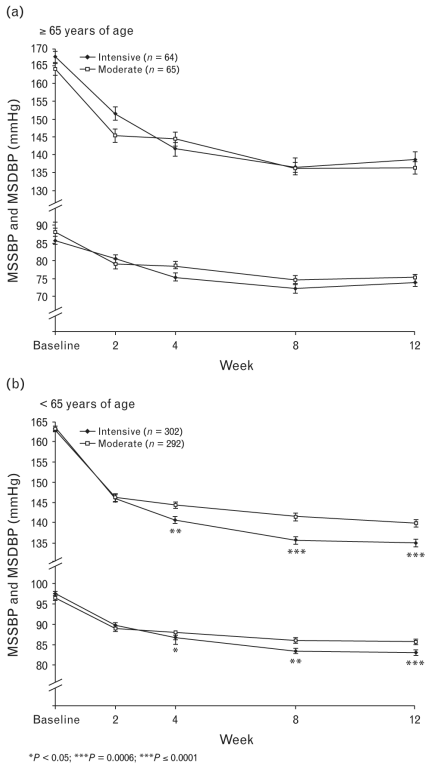

Fig. 6.

Mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) among patients at least 65 years of age (a) and below 65 years of age (b) participating in the study. Error bars represent standard error.

Table 1

Demographic and baseline characteristics

Characteristic	Intensive treatment amlodipine 10 mg/valsartan 320 mg (*n*=366)	Moderate treatment amlodipine 5 mg/valsartan 160 mg (*n*=357)
Age (years)	54.4 (11.0)	55.0 (11.0)
No. (%) ≥65 years	64 (17)	65 (18)
Sex, no. (%)		
Male	209 (57)	200 (56)
Female	157 (43)	157 (44)
Race, no. (%)		
White	235 (64)	239 (67)
Black	105 (29)	93 (26)
Other	26 (7)	25 (7)
Height (cm)	169.2 (10.5)	169.2 (10.9)
Weight (kg)	91.0 (21.9)	93.4 (24.8)
BMI (kg/m^2)	31.7 (7.0)	32.5 (7.8)
Waist circumference (cm) *	100.9 (16.4)	103.4 (15.8)
Diabetic, no. (%) †	53 (14)	65 (18)
Serum creatinine (mg/dl)	0.92 (0.2)	0.88 (0.2)
eGFR (ml/min/1.73 m^2)	91.0 (22.9)	93.4 (21.4)
Serum potassium (mEq/l)	4.2 (0.4)	4.2 (0.4)
Office sitting pulse (beats/min)	76.2 (11.9)	76.0 (12.3)
Office sitting SBP (mmHg)	163.9 (11.9)	163.3 (11.4)
Office sitting DBP (mmHg)	95.5 (11.2)	95.0 (10.3)
No. (%) patients requiring a total add on of HCTZ 25 mg ‡	127 (35)	170 (48)

Values are mean (standard deviation) unless otherwise noted. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate [Modification of Diet in Renal Disease (MDRD) method]; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

* $P<0.05$ between groups.

† Patients with medical history of diabetes, diabetic medication history, or fasting plasma glucose above 126 mg/dl and HbA1c at least 6.5% at screening.

‡ $P<0.001$ between groups.

Table 2

Number (%) of patients reporting adverse events* during the study

Event	Intensive treatment amlodipine 10 mg/ valsartan 320mg (*n*=369)	Moderate treatment amlodipine 5 mg/ valsartan 160mg (*n*=359)
Peripheral edema	32 (8.7)†	16 (4.5)
Dizziness	19 (5.1)	14 (3.9)
Headache	9 (2.4)	11 (3.1)
Fatigue	7 (1.9)	6 (1.7)
Upper respiratory tract infection	6 (1.6)	6 (1.7)
Nasopharyngitis	5 (1.4)	2 (0.6)
Nausea	5 (1.4)	5 (1.4)
Hypotension	4 (1.1)	3 (0.8)

*Reported by at least 1% of patients in the intensive treatment group.

†*P*=0.025 versus moderate treatment.