Adv Ther (2011) 28(2):134-149.
DOI 10.1007/s12325-010-0099-1

ORIGINAL RESEARCH

Real-Life Safety and Effectiveness of Amlodipine/Valsartan Combination in the Treatment of Hypertension

Irina E. Chazova · Neelesh Dongre · Alexey V. Vigdorchik

Received: October 15, 2010 / Published online: January 12, 2011

ABSTRACT

Introduction: The aim of our study was to evaluate the safety and effectiveness of the free combination of amlodipine/valsartan in patients with arterial hypertension in a real-life setting. ***Methods:*** This was a multicenter, open-label, observational, noninterventional, postmarketing surveillance study conducted in 298 centers in China, Malaysia, Pakistan, Bangladesh, Egypt, and Russia. We evaluated changes in heart rate, systolic and diastolic office blood pressure (BP), as well as BP control rate (<140/90 mmHg) overall, and in clinically relevant subgroups of hypertensive patients (BP >140/90 mmHg) after 12 weeks of treatment with 5/10 mg amlodipine and 80/160 mg valsartan combination. ***Results:*** Two thousand seven hundred and eighty-five patients with arterial hypertension were enrolled, 52 discontinued (eight due to adverse events), and four patients' data were missing. In total, 2729 patients completed the study: mean age 57.9 years, 54.5% men, 54.2% Asian, 44.6% Caucasian; 86.5% had prior hypertension treatment (which was discontinued), baseline BP was 163.1/96.2 mmHg. The significant reduction in BP (–33.2/–16.9 mmHg, $P<0.0001$) was achieved with amlodipine/valsartan treatment resulting in a final BP of 129.9/79.3 mmHg. A dose-dependent effect was observed with the least BP reduction for 5/80 mg (–29.2/–15.1 mmHg, $P<0.0001$) and the greatest for the 10/160 mg dose regimen (–43.6/–22.4 mmHg, $P<0.0001$). Treatment response increased with increasing initial severity of hypertension with the least BP reduction in patients with baseline grade 1 hypertension BP level (SBP 140-159 mmHg): –20.0/–13.4 mmHg, $P<0.0001$, and the greatest BP drops observed in grade 3 hypertensive patients with baseline systolic BP over 200 mmHg: –73.1/–26.3 mmHg, $P<0.0001$. Patients with isolated systolic hypertension had BP reductions of –24.2/–4.8 mmHg, $P<0.0001$. ***Conclusion:*** An optimal BP reduction was achieved for all hypertension grades as well as isolated systolic hypertension,

Irina E. Chazova
Department of Systemic Hypertensions,
Russian Cardiology Scientific-Industrial Complex,
Moscow, Russia

Neelesh Dongre
Novartis Pharma AG, WSJ- 27.4.45, Novartis Campus,
CH-4002 Basel, Switzerland

Alexey V. Vigdorchik (✉)
Novartis Pharma LLC, Sadovnicheskaya str.,
82/2, 115035, Moscow, Russian Federation.
Email: alexey.vigdorchik@novartis.com

providing evidence that most hypertensive patients may benefit from amlodipine/valsartan combination treatment.

Keywords: amlodipine; combination hypertension; valsartan

INTRODUCTION

High blood pressure (BP) is the world's number one cause of death,[1] with the age- and sex-adjusted prevalence varying from 28% in the North American countries to 44% in the European countries at the 140/90 mmHg threshold.[2] About 54% of strokes and 47% of ischemic heart disease worldwide are attributable to high BP according to a recently published analysis.[3] Not surprisingly, about 80% of the attributable burden of high BP disease occurs in low-income and middle-income countries, such as Asia and Pacific, Latin America, Middle East, Africa, and parts of Europe.[3] And finally it has been established that the risk of cardiovascular disease doubles with the increase of every 20/10 mmHg above a healthy BP (115/75 mmHg), providing a solid base for hypertension treatment and expansion of prevention measures in our real-life practice.[4]

Despite the availability of a wide range of antihypertensive medications, about 45.5% of treated patients in the US fail to achieve a BP control target of less than 140/90 mmHg.[5] In European countries the number of patients not reaching BP control target varies from 59.7% in England to 81.3% in Spain,[5] demonstrating substantial unmet need in the effective treatment of arterial hypertension. The situation in Eastern Europe and Asia is not that different from the western European countries and if we take Russia as one example of this region, we will see that only 21.5% of treated patients reach BP goal (20.5% men and 22.5% women) leaving 78.5% uncontrolled.[6,7] Still, these figures are far below the 54.5% control rate in the USA[5] and 40.3% in England[5] meaning that there is a very large area for improvement. Being on the lower level of BP control rate, Eastern European and Asian countries are also underrepresented in most hypertension clinical trials and very few are conducted specifically in these populations. Hence, there is a strong rationale for exploration of real-life practices in hypertension treatment in these countries and providing evidence for antihypertensive efficacy and tolerability for widely used medications by western populations in these regions.

International hypertension guidelines acknowledge that most patients will require two or more antihypertensive medications to achieve BP control, either as separate agents or in a single pill combination. One of the combinations recommended by the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines is the combination of a calcium channel blocker (CCB) and an angiotensin receptor blocker (ARB). As amlodipine is the most widely prescribed CCB and valsartan is one of the most prescribed ARBs, we conducted the present study to establish the clinical usefulness, including antihypertensive effectiveness, safety, and tolerability, of their free-dose combination in a real-life outpatient setting across Asia, Egypt, and Russia.

MATERIALS AND METHODS

Study Design and Procedures

This was a multicenter, multinational, open-label, observational, noninterventional, postmarketing surveillance (PMS) study conducted in 298 centers in Asia (China, Malaysia, Pakistan, and Bangladesh), Egypt, and Russia. Country-wide distribution of patients enrolled and who completed the study are represented in Table 1.

Table 1. Country-wise distribution of patients enrolled and who completed the trial.

Country	Patients enrolled (*n*)	Patients completed (*n*)
China	1117	1083
Russia	956	952
Egypt	272	271
Bangladesh	219	216
Pakistan	118	115
Malaysia	103	92
Total	2785	2729

The first patient was enrolled in the study on September 12, 2007 and the last patient completed the study on March 26, 2009. The current noninterventional, uncontrolled, prospective, multicenter, PMS study was conducted according to the definition of "noninterventional trials" published in the Directive 2001/20/EC of the European parliament and of the council of 4 April.[8] In accordance, the therapy was prescribed in terms of the marketing authorization; the assignment of the patient to the therapy was decided within the current practice and the medical indication and was clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures other than those usually performed were applied to the patients and epidemiological methods were solely used for the analysis of collected data. At the initial visit patient's demographic information, relevant medical history, concomitant diseases, and previous antihypertensive therapy data were collected using epidemiological methods. The dose of amlodipine/valsartan prescribed by the treating physician was also recorded at the first visit. During the course of the study, the patients were instructed not to consume any herbal formulation or any antihypertensive drug other than prescribed. Patients who were required to take medicines for any other complaints during the course of the study were allowed to take medicines only after consultation with the physician. Patients were expected to follow the diet control and exercise schedule given by the treating physician. Concomitant antihypertensive medications were allowed in the study at the discretion of the treating physician. Patients were observed over a period of 3 months (12 weeks) with approximately monthly intervals between the visits, which were not fixed but adhered to the common practice in this indication. Each patient could have come to the participating physician four times during the whole period of observation. On these visits, BP and heart rate measurements were made, documentation of antihypertensive therapy and any changes in concomitant medications was performed, and the presence and intensity of edema was evaluated. Patients were not provided study medication for the purpose of this study as their treatment was prescribed by their treating physician and this was an observational study conducted in a real-life setting. Patients could discontinue participation in the study at any moment. Premature termination of amlodipine/valsartan treatment was documented stating the date of termination and the reason for discontinuation.

Patients

The eligible population consisted of female and male adult patients suffering from arterial hypertension, who were prescribed antihypertensive therapy with the free combination of amlodipine 5/10 mg and valsartan 80/160 mg daily (recommended doses for the treatment of arterial hypertension according to the Summary of Product Characteristics). Due to the observational, noninterventional nature of the study, it was the responsibility of the treating physician to obtain the patient's oral

or written informed consent (as required by national regulations) to report his/her medical data anonymously to Novartis Pharma, in order to analyze and publish them. A patient was selected if he or she met the following criteria at baseline: male or female ≥18 years of age, systolic office BP (SBP) >140 mmHg and/or diastolic office BP (DBP) >90 mmHg, and (in the opinion of the participating physician) antihypertensive therapy with the combination of amlodipine 5/10 mg and valsartan 80/160 mg daily was indicated. This dose was subsequently prescribed to the patient by the treating physician. There were no specific exclusion criteria in this study except for contraindications mentioned in the Summary of Product Characteristics for both products. Female patients were not eligible for the study if they were pregnant, intending to become pregnant, or breastfeeding. Patients were also ineligible if they had known hypersensitivity to amlodipine/valsartan or any of the excipients in the formulation, or had severe medical condition(s) that in the view of the investigator prohibited participation in the study (eg, severe renal or hepatic impairment).

Evaluation of Outcomes

This was a noninterventional study where each participating physician conducted all required diagnostic procedures as well as all medically indicated investigations according to the routine in daily practice. The patient was followed by the same physician throughout the study as this physician was a treating physician for that patient. The following efficacy parameters were evaluated: comparison of heart rate, SBP and DBP at study start and after completion of therapy, BP control rate (<140/90 mmHg) according to international guidelines (ESH/ESC) overall and in clinically relevant subgroups. We also conducted several analyses of antihypertensive efficacy in subgroups of patients who were prescribed stable doses of amlodipine/valsartan in combination throughout the duration of study and in patients with three different hypertension grades (classified according to the SBP level), isolated systolic hypertension (ISH), as well as in patients with SBP ≥190 mmHg and ≥200 mmHg. Safety evaluation was performed by analyzing documented adverse events (AE) and serious adverse events (SAE) observed with and without causal relationship with the use of amlodipine/valsartan in combination and special analysis of the incidence of edema was conducted in order to explore dose-dependent effects of amlodipine/valsartan in combination on this established CCB side effect. The same investigators were asked to evaluate the presence and the intensity of edema in patients at baseline and on each of the follow-up visits. The severity of edema was clinically justified as mild (when there was barely perceptible pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined), moderate (when there was significantly visible pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined; however the pit thus caused disappears quickly on removal of pressure), and severe (when there is deep well-outlined pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined; the pit thus caused lasts several seconds on removal of pressure).

Statistical Analysis

The statistical analysis was performed using SAS 9.1.3. Univariate analysis of all variables was performed. Changes in BP and heart rate were mainly assessed by quantitative statistics. The analysis of variance (ANOVA) test was applied. Nominal variables such as patient and physician satisfaction survey were assessed by the chi-

square test. Bonferronis correction was used for repeated measures of analysis. Unless otherwise stated, all continuous variables, eg, age, weight, heart rate, BP, and so forth, are represented by mean and standard deviation of the mean. All the categorical variables are presented as counts and percentages. Baseline characteristics were analyzed descriptively.

RESULTS

In total, 2785 patients, prescribed amlodipine/valsartan in combination by participating physicians, entered the study. From these, only 52 patients (1.9%) discontinued the study and four patient's data was missing/incorrect, therefore 2729 patients were accepted for the final analysis. The reasons for discontinuation of the studied medication are summarized in Table 2. There was an equal distribution of men and women in the study and the majority of patients were Asian or Caucasian with similar distribution of patients between the two races (Table 3). The vast majority of patients (86.5%) received antihypertensive treatment before they were prescribed a combination of amlodipine/valsartan and the most frequently used medications included angiotensin converting enzyme (ACE) inhibitors, CCB, beta-blockers, and diuretics.

Table 2. Reasons for discontinuation of study.

Reason	*n* (%)
Discontinued Prematurely	52 (1.9)
Lost to follow-up	19 (0.7)
Patient withdrew voluntarily	12 (0.4)
Lack of efficacy	3 (0.1)
Adverse events	8 (0.3)
Patient condition no longer required valsartan/amlodipine	3 (0.1)
Others	6 (0.2)
Death	1 (0.03)

Table 3. Demographics and baseline characteristics (*n*=2729).

Demographic	Value
Age, years±SD (range)	57.86±12.45 (19-92)
Weight, kg±SD (range)	75.95±15.88 (35-152)
Sex, *n* (%)	
Men	1488 (54.5)
Women	1240 (45.4)
Data missing	1 (0.03)
Race, *n* (%)	
Asian	1478 (54.2)
Caucasian	1216 (44.6)
Black	6 (0.2)
Other	18 (0.7)
Data missing	11 (0.4)
Risk factors and concomitant diseases, *n* (%)	
Hypercholesterolemia	1294 (47.4)
Coronary heart disease	724 (26.5)
Hypertriglyceridemia	663 (24.3)
Smoking	605 (22.2)
Diabetes mellitus	570 (20.9)
Heart failure	323 (11.8)
Hyperuricemia	217 (8.0)
Respiratory disease	197 (7.2)
Others	328 (12.0)
Previous antihypertensive treatment, *n* (%)	
Yes	2361(86.5)
No	247(9.1)
Data is not available	121(4.4)
Classes of previous antihypertensive medications, *n* (%)	
ACE inhibitors	1164 (42.7)
Calcium channel blocker	1079 (39.5)
Beta-blockers	928 (34.0)
Diuretics	913 (33.5)
ARBs	360 (13.2)
Others	93 (3.4)

ACE= angiotensin converting enzyme; ARB=angiotensin receptor blocker.

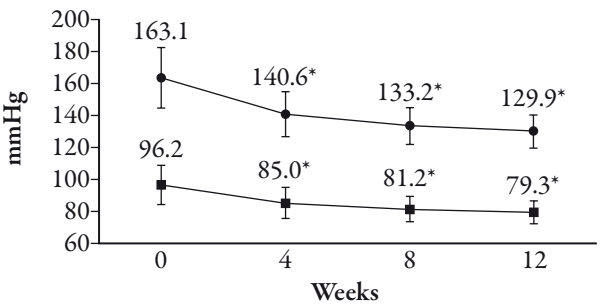
A very small percentage of patients required additional prescription of antihypertensive drugs during the course of the study. In all, 154 patients (5.6%) received beta-blockers and 100 patients (3.7%) received diuretics, concomitantly. These

data demonstrate that in the vast majority of patients, previous antihypertensive therapy was discontinued and patients were switched to amlodipine/valsartan in combination directly without any washout period. The most frequently prescribed concomitant medications were statins (19.7% patients), acetylsalicylic acid (13.1% patients), and oral hypoglycemic drugs (10.3% patients). The major reasons for concomitant medications were dyslipidemia (19.1%), ischemic heart disease (14.6%), diabetes (14.3%), and hypertension (7.0%).

Antihypertensive Efficacy

A total of 2729 patients were analyzed. Baseline BP was 163.1±18.8/96.2±12.2 mmHg and significant reductions of –33.2 mmHg SBP (P<0.0001) and –16.9 mmHg DBP (P<0.0001) were achieved during the 12 weeks of treatment with the amlodipine/valsartan combination. Final BP at the end of the study was 129.9±10.2/79.3±7.3 mmHg. As the study was conducted in a real-life setting, no washout period was possible to establish baseline BP values in enrolled patients. Hence, the baseline BP values correspond to the measurement at visit 1, and in most patients it was the BP level achieved on previous antihypertensive therapy. The significant BP reduction was already observed after the first 4 weeks of treatment (Figure 1). A total of 2155 (79.0%) patients were taking stable doses of amlodipine/valsartan, and BP reductions in these four different dose regimens are represented in Figure 2. There was a dose-dependent BP reduction of both SBP and DBP with the greatest reduction for the 10/160 mg dose regimen (–43.6/–22.4 mmHg, P<0.0001) and the least BP reduction for the 5/80 mg dose regimen (–29.2/–15.1 mmHg, P<0.0001). Regardless of the dose regimen, the mean BP of patients at the end of the study was <140/90 mmHg. BP reductions were also dependent on hypertension grade and level of SBP, with the greatest reduction observed in patients with baseline SBP ≥200 mmHg (–73.1/–26.3 mmHg),and the least BP reduction in patients with baseline grade 1 hypertension BP level (SBP 140-159 mmHg): –20.0/–13.4 mmHg (P<0.0001). In patients with ISH, SBP was reduced by 24.2 mmHg while DBP was only reduced by 4.8 mmHg. All subgroups reached a mean BP of <140/90 by the end of the study (Figure 3). The smallest BP reduction was in patients with BP level within the grade 1 hypertension range and the greatest in grade 3 hypertension patients with SBP over 200 mmHg. Patients with ISH achieved adequate SBP reduction with only minor diastolic reduction. A significant reduction of heart rate was also observed: 75.8±10.2 beats per minute (bpm) at the study start versus 73.1±7.6 bpm at the end of the study (P<0.0001). Our data show that an optimal BP reduction was achieved for all hypertension grades and for patients with ISH, providing evidence that most hypertensive patients may benefit from combination treatment with amlodipine/valsartan.

Figure 1. Mean systolic and diastolic blood pressure during the study period (mmHg). *P<0.0001 vs. baseline.



BP control rates were also evaluated in our study (Figure 4). A total of 92.9% of patients had their SBP or DBP controlled (<140 or <90 mmHg respectively). Strict BP control (BP <140/90 mmHg) was achieved in 75.6% of patients in our study. In a subgroup analysis we confirmed similar BP control rates

Figure 2. Mean reduction in systolic (SBP) and diastolic (DBP) blood pressure in patients on stable doses of amlodipine/valsartan during the study period. *P<0.0001 vs. baseline.

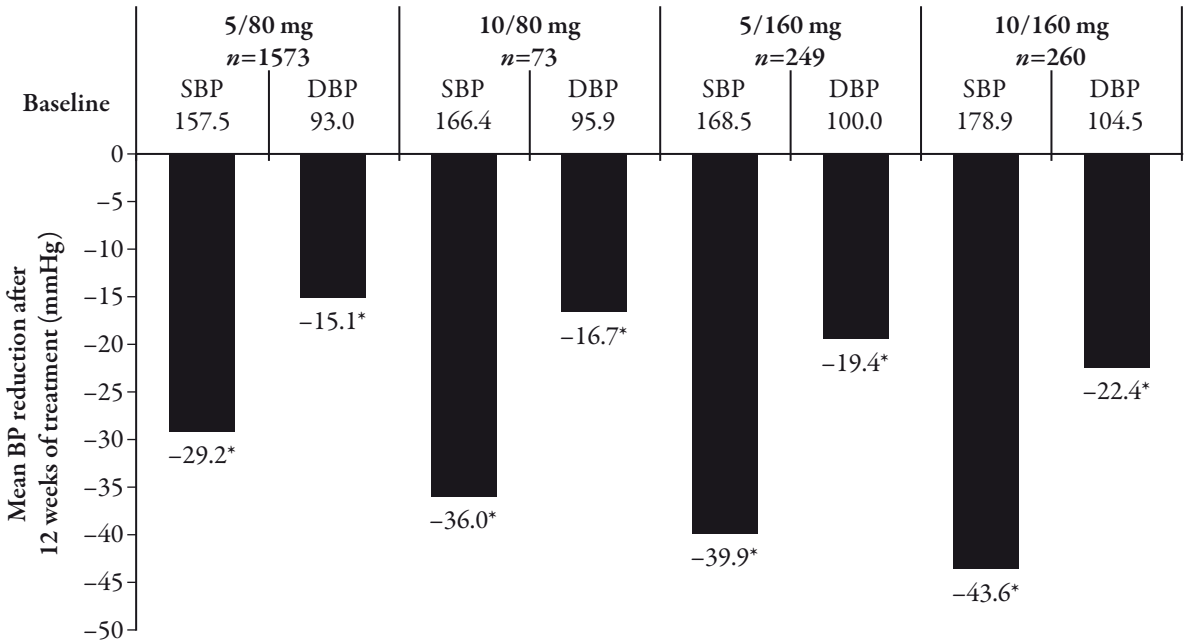
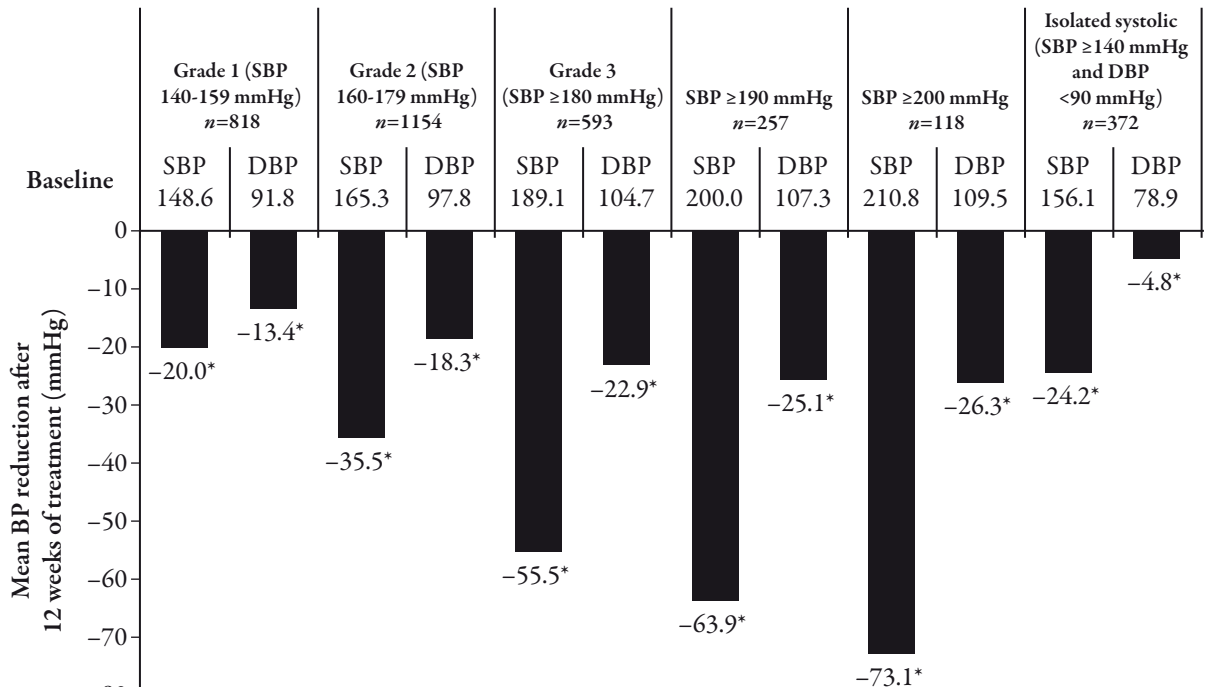


Figure 3. Mean reduction in systolic (SBP) and diastolic (DBP) blood pressure in patients with hypertension grades 1-3 and isolated systolic hypertension. *P<0.0001 vs. baseline.



(BP <140/90 mmHg) across the subgroups of patients with hypercholesterolemia, ischemic heart disease, diabetes mellitus, heart failure, and in elderly patients (≥65 years) (Figure 5).

Figure 4. Blood pressure control rates.

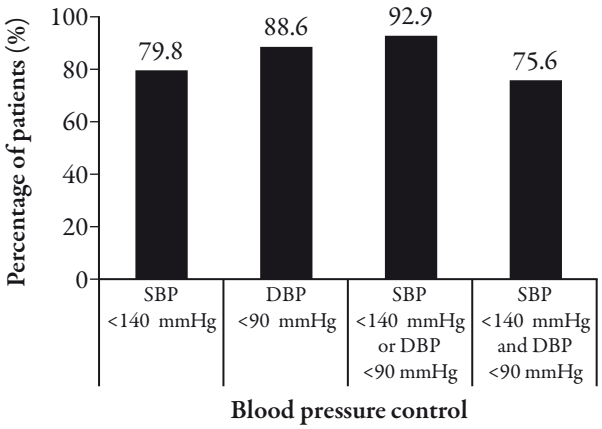
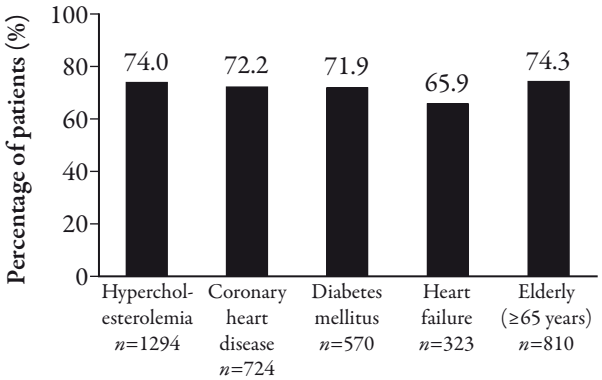


Figure 5. Blood pressure control rates in subgroups of patients.



Tolerability

The safety population of our study consisted of 2785 originally enrolled patients. Free-dose combination of amlodipine/valsartan in this 12-week study showed a very low incidence of AEs (8.8% of patients experienced AEs) and only two SAEs were reported, which were not suspected to be related to the studied treatment (Table 4). The most common reported AEs were edema, dizziness, and headache with frequency 2.3%, 1.4%, and 1.1%, respectively (Table 5).

Table 4. Summary of adverse events (AE).

	n (%)
Patients with AE	246 (8.8)
Patients having at least one AE	208 (7.5)
Patients having two AEs	30 (1.1)
Patients having more than two AEs	8 (0.3)
Total AEs in the study	293
Total serious AEs in the study	2
AEs suspected to be related to the study drug	112
AEs not suspected to be related to the study drug	181

Table 5. Adverse events.

Adverse events	*n* (%)
Edema	65 (2.3)
Dizziness	38 (1.4)
Headache	32 (1.1)
Chill	10 (0.4)
Insomnia	8 (0.3)
Cough	8 (0.3)
Rhinitis	7 (0.3)
Flushing/erubescence	6 (0.2)
Acute gastroenteritis	4 (0.1)
Abdominal pain	3 (0.1)
Anxiety	3 (0.1)
Impotence	3 (0.1)
Loose bowel movement	3 (0.1)
Nasopharyngitis	3 (0.1)
Palpitation	3 (0.1)
Vomiting	3 (0.1)
Abdominal distention	2 (0.1)
Chest distress	2 (0.1)
Epigastric pain	2 (0.1)
Fatigue	2 (0.1)
Fever	2 (0.1)
Nausea	2 (0.1)
Numbness	2 (0.1)
Pneumonia	2 (0.1)
Number of AEs that occurred once in the study	77 (2.8)
Data not available	1 (0.04)
Total	293 (10.5)

Subdural hemorrhage and pneumonia were the two SAEs reported during this study. Both SAEs resulted in death and both were not suspected to be related to the study medication. Out of these two SAEs, subdural hemorrhage was reported after the patient had already discontinued the study drug due to different AEs that happened earlier, so the death of this patient is not included in Table 2.

As edema is considered the most frequent and specific AE of CCB, we conducted an in-depth analysis of this event in our study. Out of 2729 patients, 13.7% patients experienced edema at baseline in visit 1, 12% patients had edema at visit 2, 10.7% at visit 3, and 10.1% at visit 4. The frequency of severe and moderate edema decreased and the frequency of mild edema increased during the course of the study: 72.2% of patients with edema had mild intensity, 25.1% had moderate edema, and 2.7% had severe edema at baseline before they received study medication. At the end of the study, 89.1% of patients with edema had mild intensity of edema, 10.5% had moderate edema, and only 0.4% had severe edema. This pattern was observed not only in the general population of patients but also in all subgroups of patients, who received constant doses of amlodipine/valsartan in combination throughout the study, except for the 10/80 mg dose regimen, where the total frequency of edema did not change much, but the severity of it still decreased (Table 6). The most interesting is the frequency of edema for the 10/160 mg dosing regimen. The baseline incidence of edema in this group was twice as high as in the general population or other subgroups of patients (25.4%), but it also decreased at the end of the study (17.3%). Although the CCB-caused edema could still be present in some patients at the end of our study, the use of amlodipine/valsartan in combination reduced the frequency of edema by 26.6% and the severity of edema was also reduced in our observational study. The reduction in edema frequency was the greatest in patients treated with a constant dose of 5/160 mg amlodipine/valsartan (–56.4%), followed by 5/80 mg (–40.7%), and 10/160 mg dosing regimens (–31.8%).

Table 6. Incidence of edema.

		Visit 1 *n* (%)	Visit 4 *n* (%)
All patients	Mild	270 (72.2)	245 (89.1)
n=2729	Moderate	94 (25.1)	29 (10.5)
	Severe	10 (2. 7)	1 (0.4)
	Total	374 (13.7)	275 (10.1)
10/160 mg	Mild	38 (57.6)	40 (88.9)
n=260	Moderate	24 (36.4)	5 (11.1)
	Severe	4 (6.0)	0 (0.0)
	Total	66 (25.4)	45 (17.3)
10/80 mg	Mild	3 (30.0)	10 (90.9)
n=73	Moderate	5 (50.0)	1 (9.1)
	Severe	2 (20.0)	0 (0.0)
	Total	10 (13.7)	11 (15.1)
5/160 mg	Mild	26 (66.7)	16 (94.1)
n=249	Moderate	13 (33.3)	1 (5.9)
	Severe	0 (0.0)	0 (0.0)
	Total	39 (15.7)	17 (6.8)
5/80 mg	Mild	147 (80.8)	101 (93.5)
n=1573	Moderate	32 (17.6)	7 (6.5)
	Severe	3 (1.6)	0 (0.0)
	Total	182 (11.6)	108 (6.9)

DISCUSSION

Our study demonstrated that amlodipine/valsartan in combination significantly reduces BP in patients with arterial hypertension. The BP lowering effect was dose dependant and also corresponded to the baseline level of BP elevation. These results were achieved during 12 weeks of treatment and a very small number

of AEs and SAEs were detected in a large cohort of 2785 hypertension patients. Another interesting finding in our study is that no increase in heart rate was observed, providing evidence that there was no influence of amlodipine in combination with valsartan on heart rate as one could expect. The in-depth analysis of peripheral edema incidence also showed attenuation of this well-known side effect of CCB by the addition of ARB and this tendency was evident for almost all dosing regiments of such combination.

The results of our study correspond well to the previously conducted amlodipine/valsartan randomized controlled clinical studies. Dose-dependent BP lowering by an amlodipine/valsartan combination was demonstrated by Philipp et al.[9] and further analysis performed by Smith et al.[10] confirmed that the degree of BP lowering corresponded to the initial hypertension stage. Poldermans et al.[11] study provided evidence that in patients with BP ≥180/110 mmHg amlodipine/valsartan in combination provided a SBP decrease of –43.0 mmHg and it was numerically greater than that provided by lisinopril/hydrochlorothiazide in combination in this subgroup of patients (–31.2 mmHg). This was a short study with a treatment duration of 6 weeks and a limited number of patients in this subgroup (26 patients with BP ≥180/110 mmHg); however, it was able to demonstrate a very effective reduction in BP with the use of amlodipine/valsartan in combination. In our study, a reduction of the SBP of –55 mmHg in patients with baseline BP ≥180/110 mmHg confirms that amlodipine/valsartan in combination is effective in lowering BP, but our observation period was twice as long (12 weeks) and the number of patients in this subgroup was almost 600, which may account for the differences observed between the studies.

Of course most patients will receive combination treatment after the initial monotherapy if it is not successful and an Exforge in Failure After Single Therapy (EX-FAST) study by Allemann et al. simulated such a situation.[12] It was demonstrated in this study that amlodipine/valsartan in combination provided a significant dose-dependent additional BP reduction if patients were switched from previous monotherapy with any of the major drug classes (diuretics, beta-blockers, ACE inhibitors, CCBs, ARBs). Also, the BP control rate (<140/90 mmHg) in this study was within the 77.1%-84.4% range for patients on 5/160 and the 10/160 mg doses of amlodipine/valsartan at 8 weeks and up to 87.6% in patients on 10/160 mg dose at 16 weeks (when optional hydrochlorothiazide was allowed). Our study shows similar control rates in a real-life setting, confirming these findings.

Further evidence of profound BP lowering and better control rate was presented in a nonresponders study by Trenkwalder et al.[13] In this study, patients with moderate hypertension (SBP ≥160 and <180 mmHg) who did not achieve SBP control <140 mmHg after 5 weeks of treatment with ACE inhibitor/CCB combination (ramipril/felodipine 5/5 mg) were switched to full-dose amlodipine/valsartan (10/160 mg). Only 12.8% patients achieved the target SBP with an ACE inhibitor/CCB combination and, after switching nonresponders to amlodipine/valsartan, 69.5% of them reached the target SBP after 5 weeks of such treatment. Another nonresponders study was conducted by Braun et al.[14] in patients with grade 2 hypertension (DBP 100-109 mmHg), who did not achieve DBP control (<90 mmHg) on a different free-dose CCB/ARB combination (amlodipine/olmesartan 10/20 mg). In this study only 30.4% of patients normalized DBP after 4 weeks of treatment with amlodipine/olmesartan in combination and 4 weeks' treatment with a single-pill amlodipine/valsartan combination resulted in a significant

additional BP reduction of 7.9/9.1 mmHg with 72.6% of the original non-normalizer patients achieving DBP control. In this study, heart rate also stayed largely unchanged supporting our findings. All these studies demonstrate the outstanding antihypertensive potential of the amlodipine/valsartan combination in patients not only receiving previous monotherapy, but also in patients not reaching the goal on different dual therapies.

In our study we can also find evidence of such efficacy if we look at the previous hypertension medication data. Originally, 86.5% of our enrolled patients were receiving antihypertensive medication before they were prescribed amlodipine/valsartan in combination. If we sum up the shares of different original medication classes (Table 3) we can easily see that many patients in this study were on a previous combination treatment. The absence of any washout period is a limitation of our study, but due to the real-life conditions we could not conduct an observational study with a washout period. Patients were included into the observation at the moment they were seeking treatment, so this did not create any artificial delay in prescription. We were observing a situation when a physician was facing a hypertensive patient not at goal and needed to provide a solution, ie, to prescribe an effective antihypertensive combination and get the patient to the BP goal. Still, the results of our study demonstrate that amlodipine/valsartan in combination may become such a solution in uncontrolled hypertension patients. So, although obtained in a real-life setting, we have evidence that amlodipine/valsartan in combination enables the majority of patients to control their BP below the commonly established BP goal of <140/90 mmHg (75.6%). Although we did not conduct a separate analysis of amlodipine/valsartan efficacy according to the baseline medication classes or their combinations, we can see that in a real-life setting switching to an amlodipine/valsartan combination enables very effective BP control. We also did not analyze prescription patterns of different amlodipine/valsartan dosing regimens in accordance to the baseline BP level, but we can assume that the highest doses (5/160 and 10/160 mg) were prescribed in patients with severe hypertension and the lower ones in patients with mild and moderate hypertension grades. This is supported by the fact that there was a similar number of patients who were originally prescribed and stayed on a constant dose of 5/160 and 10/160 mg amlodipine/valsartan throughout the study (509 patients, 23.6% of patients on constant dosing regimens during the course of the study) and the number of patients with hypertension grade 3 SBP level was 593 (21.7% of all patients). However, this analogy is limited and should be interpreted with caution. The lower frequency of concomitant medications (including antihypertensive) reported in our study can in part be explained by the observational nature of our study. Still, these data also support the high efficacy of amlodipine/valsartan in combination and a small need in concomitant antihypertensive support.

Our study results show that the treatment strategy using amlodipine/valsartan provides adequate BP reductions according to the patient need. The higher the patient's BP level at the start of treatment the greater the reduction in BP. Also, within the range of doses evaluated, all doses yielded a mean BP of <140/90 mmHg and the majority of patients achieved BP control. Separate analysis of patients with ISH supports this conclusion as SBP levels were substantially reduced while the already low DBP levels remained relatively unchanged.

Vasodilatory edema is a well-known and thoroughly described and understood side

effect of CCBs.[15] It has also been postulated and supported by clinical trials data that adding an ACE inhibitor or an ARB to CCBs significantly reduces vasodilatory edema via normalization of arteriolar and venular blood circulation and intracapillary pressure.[15-18] A study performed by Fogari et al.[18] used ankle-foot volume estimation (by water displacement method) to demonstrate that the addition of valsartan to amlodipine reduces CCB-induced peripheral edema.[18] The study showed that amlodipine alone caused a 23% increase in ankle-foot volume whereas the amlodipine/valsartan combination only caused 6.8% increase ($P<0.01$ vs. amlodipine). Although we used subjective clinical evaluation of the edema frequency and severity by participating physicians throughout the study, we could show that the incidence of diagnosed edema at baseline (13.7%) was not increased, which one could expect when all patients were prescribed amlodipine, but even decreased by 26.5% at the study end. The high incidence of edema at baseline in patients treated with the 10/160 mg combination (25.4%) could be explained by speculation that patients prescribed the most powerful combination were originally receiving top dose amlodipine (10 mg) and valsartan could have been added not only to reduce BP, but also to specifically reduce CCB-induced edema. Such a reduction of edema frequency and intensity is demonstrated in this subgroup of patients with no cases of severe edema at the end of the study period and three times fewer cases of moderate edema at the study end comparing to baseline. The greatest reduction of edema frequency was achieved with the 5/160 mg dose (–56.4%), and thus provides rationale for the use of this dose in patients with baseline edema who require amlodipine/valsartan in combination. Or, if edema is evident at a higher dosing regimen and requires intervention, amlodipine dose reduction looks an attractive option in this case. The reduction of severe edema cases shown for all studied dosing regimens once again proves the good tolerability profile of the combination. And finally, the very low incidence of all other AEs, with incidence of dizziness and headache less than 2% add much information to the real-life tolerability of the amlodipine/valsartan combination. Another measure of amlodipine/valsartan combination efficacy and tolerability in our study is the fact that 93.5% patients were due to have their prescription continued after the completion of the study period.

Limitations

Our study has an obvious limitation of being a nonrandomized, noncontrolled, observational study, which may limit the interpretation of our results. The real-life setting of our study does not allow us to make solid conclusions concerning comparative efficacy and tolerability of the studied combination. The subjective evaluation of edema frequency and severity is also a limitation for our study. However, the observational design of this study made it possible to acquire a large amount of data in a broad population of hypertensive patients, which makes the results of this study more relevant to real-life clinical practice.

CONCLUSION

Free-dose combination of CCB amlodipine and renin-angiotensin system blocker valsartan provided effective BP lowering which was dose dependent and corresponded to the initial degree of BP elevation. The incidence and severity of peripheral edema was reduced and the general tolerability profile of this combination was excellent. Amlodipine/valsartan combination treatment can be recommended for wide use in a variety of patients with all hypertension grades

and produces good tolerability profile with high long-term compliance potential. Nowadays, life-long hypertension treatment challenges require the use of effective and well-tolerated combinations of medications in order to satisfy every single patient's needs. This could create a basis for positive changes in global cardiovascular mortality and morbidity reduction, especially in the regions with originally poor BP control, like Asia and western Europe.

ACKNOWLEDGMENTS

This study was sponsored by Novartis Pharma. Irina Chazova is a consultant for Novartis Pharma LLC, Russia, and has received grant support from Novartis Pharma LLC, Russia. Neelesh Dongre and Alexey Vigdorchik are employees of Novartis Pharma. Alexey Vigdorchik is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

The authors thank the participating physicians: Bangladesh: Dr. Abu Tarek Iqbal, Dr. Aminur Rahman Laskar, Dr. Biswa Nath Podder, Dr. Borhan Uddin Ahmed, Dr. Ferdous Hassan Apu, Dr. Gautam Kumar Roy, Dr. Golam Mostafa, Dr. Haryati Hamzah, Dr. Ibrahim Chowdhury, Dr. Juhaida Binti Daud, Dr. Khawaja Nazim Uddin, Dr. Mahbubur Rahman, Dr. Mazharul Islam, Dr. Mizanur Rahman, Dr. Ninin Sukminingrum, Dr. Rauf, Dr. Sahabul Huda Chowdhury, Dr. Serajul Haque, Dr. Shaheen Ahmed, Dr. Uttam Kumar Saha. China: Dr. Peng Chen, Dr. Cai Jingjing, Dr. Cao Liou, Dr. Chen Jun, Dr. Chen Zhi Fu, Dr. Chunxuan Hua, Dr. Cuiling Sun, Dr. Fang Zhang, Dr. Guo Liang Xiong, Dr. Hailei Zhang Dr. Haiyun Liu, Dr. Hong Cai, Dr. Hong Chen, Dr. Hong Yong Dun, Dr. Huang Kan, Dr. Huayun Zhao, Dr. Hui Wu, Dr. Jia Wen Yong, Dr. Jiabao Zhang, Dr. Jiandi Wu, Dr. Jiangui He, Dr. Jiangzi Yuan, Dr. Jianjie He, Dr. Jie Ji, Dr. Jin Bai, Dr. Jin Chen, Dr. Jing Zhuang Mai, Dr. Jun Yang, Dr. Junru Yan, Dr. Kaiyuan Zhu, Dr. Lan Zhu, Dr. Li Dandan, Dr. Li Jia Nan, Dr. Li Jing, Dr. Li Xiao, Dr. Li Yue Hua, Dr. Lili He, Dr. Ling Chen, Dr. Linlin Mai, Dr. Liu Xiao Hong, Dr. Lu Qui Fen, Dr. Min Li Zhu, Dr. Minmin Xu, Dr. Na Liu, Dr. Nan Jing Du, Dr. Nanjin Du, Dr. Ning Xu, Dr. Ping Zheng, Dr. Qian Ying, Dr. Qing Gu, Dr. Ren Hong, Dr. Ren Yan Ni, Dr. Rong Li, Dr. Shan Mou, Dr. Shengming Fang, Dr. Shengming Fang, Dr. Shi Hao, Dr. Shuixiang Yang, Dr. Shuyan Chen, Dr. Sifeng Li, Dr. Sun Linlin, Dr. Tian Hai Ling, Dr. Wang Hai Yan, Dr. Wang Minghua, Dr. Wang Qian, Dr. Wangxiang Yan, Dr. Wei Fang, Dr. Wei Wu, Dr. Weiping Chen, Dr. Weiyi Li, Dr. Weiyi Mai, Dr. Wenze Hu, Dr. Wu Yong Yi, Dr. Xia Jing Che, Dr. Xiaoqing Liu, Dr. Xu Chen Gang, Dr. Xu Chen Hua, Dr. Xu Sheng Zhou, Dr. Xu Yu Shen, Dr. Xuexin Liao, Dr. Yafei Jin, Dr. Yafei Jin, Dr. Yan Fang, Dr. Yan Peng, Dr. Yan Wang, Dr. Yang Han, Dr. Yanshou Huang, Dr. Yanxian Wu, Dr. Yi He, Dr. Yi Jun Zhou, Dr. Yi Wu, Dr. Yin Che Chen, Dr. Ying Shen, Dr. Yingping Liu, Dr. YinZhong Bu, Dr. Yong Wu, Dr. Youqin Ding, Dr. Youqin Wang, Dr. Yugang, Dr. Yun Cai, Dr. Yun Liu, Dr. Yuqin Wang, Dr. Yuying Chen, Dr. Zepeng Lin, Dr. Zhang Min, Dr. Zhang Wen, Dr. Zhang Yachen, Dr. Zhinan Wang, Dr. Zhizhen Zheng, Dr. Zhu Chao Hui. Egypt: Dr. Ali Abdel Rehim, Dr. Abbass Oraby, Dr. Adel Mohamed Kamal El Etriby, Dr. Ahmed Shafie Ammar, Dr. Aliaa Abdel Fattah, Dr. Aly Abassy, Dr. Ashraf Badawi, Dr. Ashraf Okba, Dr. Eman Ahmed Zaatout, Dr. Hossam El Hossary, Dr. Khalifa Mahmoud Abdallah, Dr. Mohamed Abdel Ghany, Dr. Mohamed Sobhy, Dr. Mohamed Tawfik Khattab, Dr. Mohamed Wafaie, Dr. Mostafa Nawwar, Dr. Ramez Guindy, Dr. Samir Helmy Assaad. Malaysia: Dr. Alan Fong Yean Yip, Dr. Anandan Subramaniam, Dr. Anwar Rapaee, Dr. Aziz Al-safi Ismail, Dr. Chang Boon Cheng, Dr. Chua Seng Keong, Dr. Fam Chee Kwong, Dr. Juhaida Binti Daud, Dr. Juwita Shaaban, Dr. Keng Tee Chan, Dr. Kunjithapatham Balasubramaniam,

Dr. Liew Houng Bang, Dr. Mohazmi Mohamad, Dr. Ninin Sukminingrum, Dr. Nor Hanim, Dr. Norwati Daud, Dr. Ong Tiong Kiam Dr. Rusni Dollah, Dr. Sim Kui Hian, Dr. Tengku Mastura Mohd, Dr. Valar Mathi, Dr. Vijay Ananda, Dr. Wan Syaheedah Van Ghazali, Dr. Yew Kuan Leong, Dr. Haryati Hamzah. Pakistan: Dr. Asif Raza, Dr. M. Zaman Saikh, Dr. Feroz Memon, Dr. Irfan Ahmed, Dr. Irfan Ijaz. Russia: Dr. Abazova IM, Dr. Abdolieva SA, Dr. Abramova NA, Dr. Adamov VI, Dr. Agapova VI, Dr. Agoeva MB, Dr. Akhtyamov MN, Dr. Alekseeva, Dr. Alexandrova VN, Dr. Alferova IV, Dr. Andreeva EI, Dr. Andriyanov MT, Dr. Arkhipova YV, Dr. Arsenieva OA, Dr. Artamonova YV, Dr. Avdeeva OV, Dr. Bagdulina EN, Dr. Balkova SF, Dr. Barbarin IN, Dr. Bataeva, Dr. Belaya VA. Dr. Belovolova TI, Dr. Berezina EG, Dr. Bezludova EA, Dr. Bogomolova SV, Dr. Bogorodsky OM, Dr. Borodulina NA, Dr. Bugaetc LG, Dr. Bugrov VY, Dr. Bushmakina LY, Dr. Chaadaeva MI, Dr. Chubukova NA, Dr. Chugunova IV, Dr. Chumakova EV, Dr. Didenko OI, Dr. Dikareva TV, Dr. Djha OO, Dr. Dudieva MG, Dr. Dulepova AA, Dr. Durnikova OI, Dr. Dvornikov VE, Dr. Efimova NV, Dr. Eliseeva NP, Dr. Enikeeva GR, Dr. Eremenko IA, Dr. Erokhina TA, Dr. Evdokimova OV, Dr. Evstigneeva LP, Dr. Fedotova NG, Dr. Galushkov SV, Dr. Gerasimova OA, Dr. Gimadeeva RI, Dr. Glotko NA, Dr. Glushenko NP, Dr. Golotvin MV, Dr. Gorbacheva EV, Dr. Gorbunova EN, Dr. Gravelsin TY, Dr. Gridneva AV, Dr. Grigoryan CA, Dr. Guseva YG, Dr. Hachaturyan LE, Dr. Harnetova NP, Dr. Hlebosolova NB, Dr. Ignatieva TG, Dr. Ilyinikh EA, Dr. Ivanenko VV, Dr. Ivanyushina NI, Dr. Ivochkina MI, Dr. Ivolgin EM, Dr. Kaledin OL, Dr. Kalinin MN, Dr. Kalivo OL, Dr. Karaguzina TN, Dr. Karandasova TM, Dr. Karmanova IV, Dr. Karpova OG, Dr. Karpuk VI, Dr. Kartina NP, Dr. Kazanskaya EM, Dr. Kirakozov DA, Dr. Komarov AA, Dr. Komarova NA, Dr. Komelov VN, Dr. Koreshkina MI, Dr. Korotina NV, Dr. Kovaleva NA, Dr. Kulakova LA, Dr. Kulibaba SA, Dr. Kutuzova SA, Dr. Kuznecova TV, Dr. Larionova AP, Dr. Latipova LF, Dr. Lazurina IE, Dr. Leonidova AZ, Dr. Levshin AV, Dr. Lisenko MN, Dr. Lisina SV, Dr. Lopikhina MD, Dr. Lukina EY, Dr. Maklakova MP, Dr. Mamakova LR, Dr. Maneeva ID, Dr. MazankoOE, Dr. Melnikova LA, Dr. Melnikova SV, Dr. Mironova EE, Dr. Mishenko NG, Dr. Mitrokhina TV, Dr. Mitroshina TN, Dr. Mokievskaya AN, Dr. Molchanova IV, Dr. Morozov SL, Dr. Moserova EM, Dr. Mukhamedrakhimova AR, Dr. Musurok TP, Dr. Muzalevskiy II, Dr. Nabiullina TA, Dr. Nikonorova NN, Dr. Oleinikova NV, Dr. Perkova EM, Dr. Permyakova OV, Dr. Petrov EV, Dr. Petrova AF, Dr. Petrushevskaya SV, Dr. Plakhova SP, Dr. Podbolotova AV, Dr. Pospelova NV, Dr. Pozdnyakova OS, Dr. Priyateleva MY, Dr. Pronina NN, Dr. Pukhova MB, Dr. Rachinskaya ZV, Dr. Rasskazova, Dr. Repkina YV, Dr. Ribakova TV, Dr. Ribalchenko EV, Dr. Ribinskaya AN, Dr. Romanenko VV, Dr. Rozbickaya II, Dr. Rumyantsev NV, Dr. Rustamova ZS, Dr. Ryazanceva LG, Dr. Ryzhkova ES, Dr. Salukhov VV, Dr. Savelyeva NY, Dr. Semukhina EN, Dr. Sevodina RK, Dr. Shabalina EG, Dr. Sharafeev RR, Dr. Shashkova TV, Dr. Shekanova, Dr. Shelekhova MB, Dr. Sherbak MF, Dr. Shimanenko SE, Dr. Shlyapkin SN, Dr. Shmeleva EV, Dr. Shurkevich NP, Dr. Shvecova IA, Dr. Sidorov DV, Dr. Silantieva LB, Dr. Skudarnova TV, Dr. Smirnova, Dr. Sokol NI, Dr. Sokolov AI, Dr. Solomko LM, Dr. Sosnina GV, Dr. Stolyarova NI, Dr. Streltcova OV, Dr. Strogalova VN, Dr. Strokina TK, Dr. Sukhoroslova TA, Dr. Suslikov, Dr. Svinina SA, Dr. Tarlovskaya EI, Dr. Tcvetkova LA, Dr. Tishkevich SN, Dr. Trapeznikova EV, Dr. Trufanova NV, Dr. Tyurina IA, Dr. Uzdenova AB, Dr. Vakhrulina NK, Dr. Valikulova FY, Dr. Varnakova LN, Dr. Vasileva EN, Dr. Vasilieva LB, Dr. Velizhanina IA, Dr. Verkhoturova OA, Dr. Verkhovskaya VA, Dr. Vershinina AM, Dr. Vetrova IP, Dr. Vlasova OV, Dr. Voronkova NB, Dr. Yakovleva NM, Dr. Yanbaeva SM, Dr. Yanina YA,

Dr. Yamilova AG, Dr. Yashina LM, Dr. Zaharova YV, Dr. Zapolskih LG, Dr. Zaytsev YE, Dr. Zaytseva NB, Dr. Zhevagina IA, Dr. Zhukova EV, Dr. Zorina EN, Dr. Zubatkina TN, Dr. Zubeeva GN.

REFERENCES

1. Mancia G, Laurent S. Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27:2121-2158.

2. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003;289:2363-2369.

3. Lawes C, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008;371:1513-1518.

4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-1913.

5. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States Hypertension. 2004;43:10-17.

6. Shalnova SA, Balanova YA, Konstantinov VV, et al. Arterial hypertension: prevalence, patients' awareness, treatment patterns and efficacy among Russian Federation population. Russian Cardiology Journal. 2006;4:45-51.

7. Shalnova SA, Deev AA, Oganov RG. Monitoring arterial hypertension in Russia. Circulation. 2006;113:f83-84.

8. Directive 2001/20/EC of the European parliament and of the council of 4 April on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities. 2001;121:34-44.

9. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007;29:563-580.

10. Smith TR, Philipp T, Vaisse B, et al. Amlodipine and valsartan combined and as monotherapy in stage 2, elderly, and black hypertensive patients: subgroup analyses of 2 randomized, placebo-controlled studies. J Clin Hypertens (Greenwich). 2007;9:355-364.

11. Poldermans D, Glazes R, Kargiannis S, et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared with lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. Clin Ther. 2007;29:279-289.

12. Allemann Y, Fraile B, Lambert M, Barbier M, Ferber F, Izzo J. A randomized, double-blind, multicenter study to evaluate the efficacy of the combination of amlodipine and valsartan in hypertensive patients uncontrolled on previous monotherapy: the EX-FAST Study. J Clin Hypertens. 2008;10: 185-194.

13. Trenkwalder P, Schaetzl R, Borbas E, Handrock R, Klebs S. Combination of amlodipine 10 mg and valsartan 160 mg lowers blood pressure in patients with hypertension not controlled by an ACE inhibitor/CCB combination Blood Pressure. 2008;17(suppl. 2):13-21.

14. Braun N, Ulmerb H.-J, Ansaric A, Handrock R, Klebs S. Efficacy and safety of the single pill combination of amlodipine 10 mg plus valsartan 160 mg in hypertensive patients not controlled by amlodipine 10 mg plus olmesartan 20 mg in free combination. Curr Med Res Opin. 2009;25:421-430.

15. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Curr Cardiol Rep. 2002;4:479-482.

16. Jamerson K, Nwose O, Jean-Louis L, Schofield L, Purkayastha D, Baron M. Initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior

blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 hypertension. Am J Hypertens. 2004;17: 495-501.

17. Schrader J, Salvetti A, Calvo C, et al. The combination of amlodipine/valsartan 5/160 mg produces less peripheral oedema than amlodipine 10 mg in hypertensive patients not adequately controlled with amlodipine 5 mg. Int J Clin Pract. 2009;63:217-225.

18. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens. 2007; 21:220-224.