The efficacy and safety of single-pill combinations of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/hydrochlorothiazide (Valtricom®) in patients with grade 2 or 3 arterial hypertension – VICTORY II clinical trial.

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Key words
Hypertension, single-pill combination (SPC), valsartan, amlodipine, blood pressure (BP), hydrochlorothiazide

Abstract

Background: *In spite of optimisation and simplification of hypertension treatment, the achievement of blood pressure (BP) control is still a challenge, with most of the patients requiring combination treatment to achieve target BP control. Due to the multifactorial effect of hypertension, along with the BP lowering effect, additional organ-protective properties of antihypertensive therapy are beneficial for the optimal reduction of cardiovascular risk.*

Objectives: *The primary objective of the multicentre, open, prospective VICTORY II clinical trial was to evaluate the percentage of patients who reached the office BP target levels after 16 weeks of therapy with single-pill combinations (SPC) of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/hydrochlorothiazide (HCTZ) (Valtricom®) in naïve or previously treated but uncontrolled hypertensive individuals with grade 2 or grade 3 hypertension, and to assess the safety of the tested medicines. The secondary objectives were to assess the effect of tested medicines on achieving the target levels of 24h ambulatory BP monitoring (24h ABPM) and home BP monitoring (HBPM), together with the effect on metabolic parameters, the level of albuminuria, elasticity of arteries, and the endothelial function. Additionally, the effects on erectile function in men, effects on the quality of life, and the convenience of the studied medicines for patients were investigated.*

Methods: *All patients (men and women aged ≥ 18 years) started the treatment with SPC of amlodipine and valsartan. If necessary, treatment could be up-titrated step by step to the final option, i.e. triple SPC of amlodipine/valsartan/HCTZ to achieve target BP levels. Multiple strengths of the studied medicines were used for convenient up-titration. The total active treatment duration was 16 weeks, divided into four treatment periods, with an additional week for further examinations in a subgroup of patients.*

Results: *The results of the VICTORY II trial, in which 100 patients were included in the active phase, showed that SPCs of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide effectively reduce BP in patients with grade 2 or 3 hypertension. After 16 weeks of therapy, the target office BP was achieved in 90% of the patients together with a good therapy tolerability*

profile. According to the 24h ABPM, the target levels of mean daily SBP/DBP were reached by 52.9%/67.6% of the patients, respectively. The proportion of the patients reaching the target home BP levels according to the HBPM diary was 40.2%. The speed of pulse wave velocity (PWV) improved in 66.7% of the patients. At least 5% reduction of central (aortic) BP was seen in 73% of the patients. In 58.8% of the patients, a decrease of albuminuria was observed. The treatment also showed a positive effect on the erectile function in men and improvement in the quality of life, and was considered by the patients as more convenient than their previous antihypertensive therapy.

Conclusion: *The treatment of hypertension with the amlodipine/valsartan-based SPCs (SPC of amlodipine/valsartan or amlodipine/valsartan/HCTZ) offers an effective, safe, and convenient strategy to control BP in patients with grade 2 and grade 3 hypertension, offering additional positive effects on the target organ function, erectile function, and the quality of life.*

Based on the following already published articles:
Chazova IE, Martynyuk TV, Rodnenkov OV et al. First results of Russian multicenter prospective clinical study VICTORY II: Vamloset® and Co-Vamloset effectiveness and safety in patients with stage 2 and 3 arterial hypertension. Systemic Hypertension. 2020;17(2): 36–47. DOI: 10.26442/2075082X.2020.2.200123;
Chazova IE, Martynyuk TV, Rodnenkov OV et al. Implementation of the organoprotective properties of fixed combinations of valsartan, amlodipine and hydrochlorothiazide (Vamloset® and Co-Vamloset) in patients with grade 2 and 3 hypertension in the Russian clinical study VICTORY II. Systemic Hypertension. 2020; 17 (3): 59–70. DOI: 10.26442/2075082X. 2020.3.200414;
Martynyuk TV, Chazova IE on behalf of investigator team. Aspects of efficacy, safety and adherence to antihypertensive therapy with single pill combinations of valsartan, amlodipine and hydrochlorothiazide (Vamloset® and Co-Vamloset) in patients with 2 and 3 grade of arterial hypertension in the Russian clinical study VICTORY II. Systemic Hypertension. 2021; 18 (1): 50–62. DOI: 10.26442/2075082X.2021.1.200736.

Introduction

The main goal of hypertension treatment is to minimise the risk of fatal and non-fatal cardiovascular (CV) complications, cerebrovascular complications, and chronic kidney disease (CKD).[1] The treatment of hypertension to the target BP levels (< 140/90 mmHg) provides significant protection against CV events with incremental benefits of intensive treatment to target BP levels ≤ 130/80 mmHg or lower, if tolerated, but not below 120 mmHg[1] in patients at higher risk (concomitant vascular disease, renal disease, diabetes etc.).[2] In spite of many different recommendations for screening and proper management of hypertension, reaching BP target levels is still a challenge in clinical practice.[1, 3] In Europe, according to published data, 47% of treated patients in primary prevention[4] and 42% in secondary prevention[5] do not achieve office BP target levels.

The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of arterial hypertension recommend that antihypertensive treatment be initiated with a two-medicine combination, preferably in the form of an SPC, to improve treatment compliance. Angiotensin receptor blockers (ARBs) are among the five major classes of medicines that form the basis of antihypertensive therapy. Among the recommended first-line medicines are also ARBs (e.g. valsartan) in combination with a calcium channel blocker (CCB) or a diuretic, preferably in the form of an SPC.[1] The most recent 2020 International Society of Hypertension (ISH) guidelines for the management of hypertension favour the use of an SPC of renin-angiotensin-aldosterone system inhibitors (RAASi) with dihydropyridine CCB over SPC of RAASi with diuretics as the initial treatment of hypertension.[6] Nevertheless, about one third of hypertensive patients still need to be treated with more than two antihypertensive medicines to achieve BP control.[7] For those, the logical option enforced also by the guidelines is to increase treatment to a three-medicine combination therapy of a RAASi, CCB, and diuretic, preferably in the form of an SPC.[1, 6] Combination therapy has a simultaneous effect on various physiological systems. Treatment with an SPC may increase treatment adherence and show additional synergistic vasoprotective or pleiotropic effects. Therefore, it may lead to more adequate and quicker control of BP.[1, 8]

In the management of hypertension, the efficacy of the treatment is mostly assessed by office BP values. The use of out-of-office BP measurement with 24h ABPM and/or HBPM as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension, and monitor BP values, is also recommended in the current ESC/ESH guidelines.[1] Besides, HBPM has recently gained in importance due to COVID-19 pandemic restrictions and reduced/limited patients' visits to doctors' office.

The treatment of hypertension is not only important to reduce increased BP levels, but to also reduce hypertension-mediated damage of target organs (HMOD), such as heart, brain, retina, kidney, and vasculature.[1] Hypertension itself can increase arterial stiffness and endothelial dysfunction.[9] Carotid-femoral pulse wave velocity (PWV) is the gold standard for measuring the large artery stiffness.[1] Low-grade inflammation and oxidative stress is connected to hypertension-induced endothelial dysfunction.[10] Therefore, any positive effect of an antihypertensive medicine on inflammatory markers may be beneficial for the reduction of inflammation, leading to the improvement of atherosclerosis and endothelial function of the vessel.[10, 11]

We present the results from the VICTORY II trial, where office BP, 24h ABPM and HBPM were used to assess the efficacy of SPCs of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/HCTZ (Valtricom®) in naïve or previously treated but uncontrolled individuals with grade 2 or 3 hypertension. The effects on the selected parameters involved in the vessel and kidney function, together with the effect on metabolic parameters and different aspects of patient's quality of life were also assessed.

Methods

Trial design

The VICTORY II clinical trial was a multicentre, open, prospective clinical trial. It included patients with grade 2 or 3 arterial hypertension older than 18 years, previously untreated, with office SBP ≥ 160 mmHg and/or office DBP ≥ 100 mmHg, or those with uncontrolled office BP by previous mono- or double antihypertensive therapy. The total active treatment duration was 16 weeks.

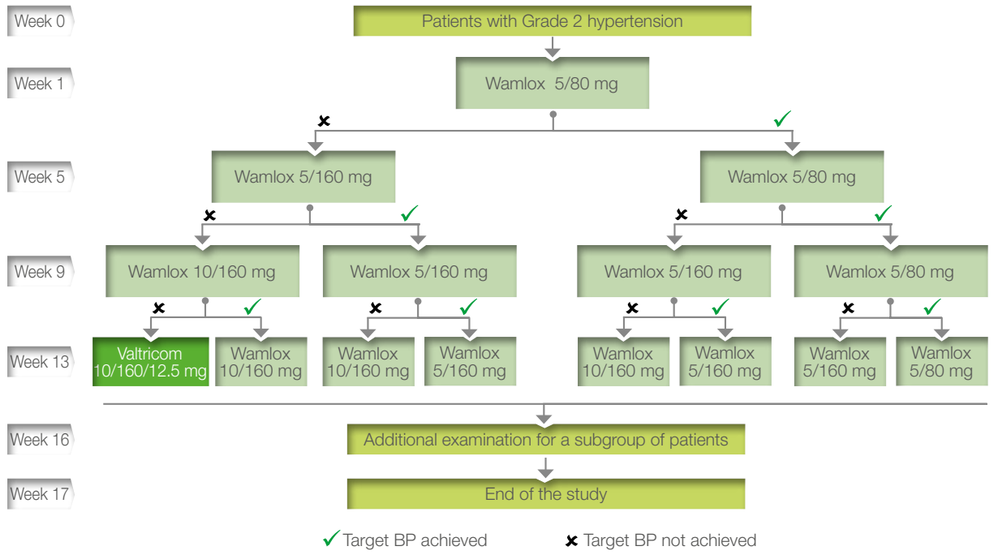
The patients were required to visit clinical centre in 4-week intervals. Each patient had to participate in five visits. The screening visit was followed by an initial visit (Visit 1), three follow-up visits at week 5 (Visit 2), week 9 (Visit 3) and week 13 (Visit 4), and a final visit at week 17 (Visit 5). A subgroup of patients had an additional visit at week 16 (Visit 5a) for additional examinations for the purpose of installing devices for 24h ABPM.

Trial exclusion criteria included contraindications to any component of the dual or triple SPC, and conditions that need to be treated with caution. The patient's inability to comply with the

requirements of the trial protocol regardless of the reason, and any other reasons that, in the opinion of the investigator, prevent the patient from successfully participating in the trial. For women with childbearing potential it was mandatory to use an adequate method of contraception throughout the trial. Patients were not randomised.

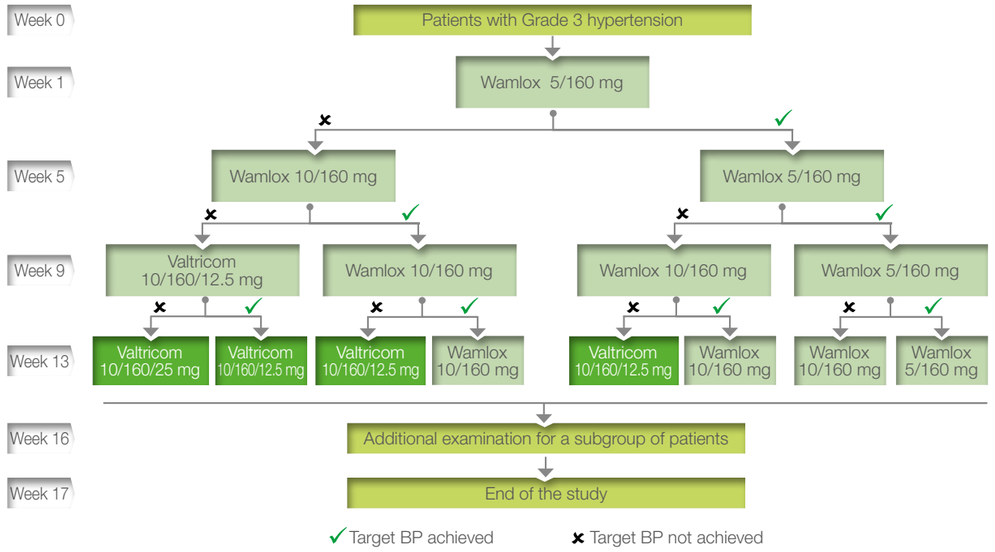
The primary endpoint was to evaluate the percentage of patients who reached the target office BP levels after 16 weeks of therapy with the SPCs of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/HCTZ (Valtricom®). The secondary endpoints were the effect of the amlodipine/valsartan-based therapies on the level of decrease in BP after 16 weeks and the percentage of the patients reaching target BP levels according to HBPM. In a subgroup of patients, we additionally evaluated the percentage of the patients reaching target BP levels by 24h ABPM, the effect of studied medicines on the central aortic pressure, elasticity of arteries (values of PWV and augmentation index), endothelial function (levels of tumour necrosis factor α (TNFα), interleukins 6 (IL-6) and 10 (IL-10), vascular cell adhesion molecules type 1 (sVCAM-1), and vascular endothelial growth factor (VEGF -A)). Furthermore, the effect of the studied medicines on the metabolic parameters, the level of albuminuria, erectile function in men, the quality of life, and the convenience of therapy for all patients were also investigated.

At Visit 1, all the patients with grade 2 hypertension started the treatment with the SPC of amlodipine/valsartan (Wamlox®) 5/80 mg, which could be up-titrated to the SPC of amlodipine/valsartan/HCTZ (Valtricom®) 10/160/12.5 mg, to achieve target office BP (Figure 1). The patients with grade 3 hypertension started the treatment with the SPC of amlodipine/valsartan (Wamlox®), 5/160 mg, which could be up-titrated to amlodipine/valsartan/HCTZ (Valtricom®) 10/160/25 mg, to achieve target office BP (Figure 2). At monitoring visits, the decision about the correction of the antihypertensive medication was made by the physician based on the analysis of office BP measurement results, data from HBPM diary, physical examination, general condition, and patient's complaints.



Wamlox: dual combination of amlodipine/valsartan; Valtricom: triple combination of amlodipine/valsartan/HCTZ

Figure 1: Trial treatment flow chart for the patients with grade 2 hypertension.



Wamlox: dual combination of amlodipine/valsartan; Valtricom: triple combination of amlodipine/valsartan/HCTZ

Figure 2: Trial treatment flow chart for the patients with grade 3 hypertension.

Evaluations

All patients started the trial with the initial screening visit performed to verify eligibility. A complete medical history, physical examination, laboratory analysis including pregnancy test in women with childbearing potential, BP measurement, and electrocardiography (ECG) were performed.

Office SBP and DBP were measured at every visit in all the patients. For HBPM, at Visit 1, all the patients were given automatic BP monitors and diaries for self-monitoring of BP, which the patients filled out independently according to the recommendations. 24h ABPM was measured in a subgroup of the patients at Visit 1 before the administration of the studied medication and at Visit 5.

To examine the effect of the treatment on the elasticity of arteries, the measurement of PWV, central (aortic) BP and determination of the augmentation index were performed in a subgroup of the patients before the administration of the studied medication (Visit 1) and at Visit 5 of the study using the SphygmoCor device. In addition, the levels of different parameters related to endothelial function (TNFα, IL-6, IL-10, sVCAM-1, VEGF-A) were assessed in a subgroup of the patients before the administration of the tested medicines at Visit 1 and at Visit 5.

To assess organ-protective properties of the tested medicines, the level of albumin in urine was determined in all the patients at the screening visit and at Visit 5. In addition, the assessment of the erectile function and of the quality of life was done using the International Index of Erectile Function (IIEF-5) and S36-Item Short Form Survey (SF-36) questionnaire, which was filled in by the patients at Visit 1 and at the end of the trial at Visit 5.

The overall clinical effectiveness of the tested medicines was evaluated at the end of the treatment in accordance with the criteria based on the achieved office BP levels, and the presence and severity of adverse events (AE) with the following gradation:

- Extremely high (office BP reduced to 139/89 mmHg (139/84 mmHg in patients with diabetes mellitus) or lower values in the absence of adverse events (AE)),

- Very high (office BP reduced to 139/89 mmHg (139/84 mmHg in patients with diabetes mellitus) or lower values, in the presence of pulmonary AEs that did not require discontinuation of the trial medication),
- High (office SBP was reduced by at least 10 mmHg, while office DBP was reduced by at least 5 mmHg, AEs being absent),
- Satisfactory (office SBP was reduced by at least 10 mmHg and office DBP was reduced by at least 5 mmHg with AEs of moderate severity that did not require withdrawal of the tested medicines; or a reduction was achieved only in office SBP by at least 10 mmHg or only in office DBP by at least 5 mmHg without AEs of mild or moderate severity, which did not require withdrawal of the tested medicine), and
- Unsatisfactory (the patient developed AEs, requiring the discontinuation of the trial medication, or office SBP was reduced by less than 10 mmHg or office DBP was reduced by less than 5 mmHg).

Results

Baseline characteristics of the participants

The trial included 100 patients: 59 women and 41 men with grade 2 (60 patients) and grade 3 (40 patients) hypertension. The average age of patients was 59.5 ± 10.9 years, with a duration of hypertension of 83.4 ± 8.4 months. The trial population profile is presented in Table 1. Groups of patients with grade 2 and 3 hypertension were comparable in age, gender, duration of hypertension, and body mass index (BMI).

	Grade 2 hypertension group	Grade 3 hypertension group	All patients
No. (number)	60	40	100
Age (years) (average ± SD)	60.0 ± 10.6	58.7 ± 11.4	59.5 ± 10.9
Male, No. (%)	22 (36.7%)	19 (47.5%)	41 (41.0%)
Female, No. (%)	38 (63.3%)	21 (52.5%)	59 (59.0%)
Caucasian race, No. (%)	60 (100%)	40 (100%)	100 (100%)
Duration of hypertension, (months) average ± SD	83.8 ± 11.6	82.7 ± 1.9	83.4 ± 8.4
Body mass index (kg/m^2) average ± SD	30.5 ± 5.4	29.5 ± 4.5	30.1 ± 5.1

SD – standard deviation

Table 1: Demographic characteristics of the trial participants at baseline.

The concomitant diseases in patients included in the trial are presented in Table 2. In addition to hypertension, 41% of the patients had dyslipidaemia. Obesity was observed in 32% of patients; 13% of patients were smokers. Fasting hyperglycaemia and impaired glucose tolerance were detected in 7% and 3% of the patients, respectively. Type 2 diabetes was observed in 11% of the patients. Atherosclerosis was present in 3% of the patients in peripheral arteries and in 11% of the patients in the aorta or brachiocephalic arteries. As many as 11% of the patients suffered from chronic heart failure and 7% of the patients had angina pectoris.

	Grade 2 hypertension group No. (%)	Grade 3 hypertension group No. (%)	All patients No. (%)
Dyslipidaemia/hypercholesterolaemia	21 (35.0%)/9 (15.0%)	20 (50.0%)/3 (7.5%)	41 (41.0%)/12 (12.0%)
Obesity	20 (33.3%)	12 (30.0%)	32 (32.0%)
Endocrine disorders	11 (18.3%)	1 (2.5%)	12 (12.0%)
Cardiac conduction and heart rhythm disorder	9 (15%)	2 (5.0%)	11 (11.0%)
Chronic heart failure	5 (8.3%)	6 (15.0%)	11 (11.0%)
Diabetes mellitus, type 2	5 (8.3%)	6 (15.0%)	11 (11.0%)
Fasting hyperglycaemia/impaired glucose tolerance	5 (8.3%)/3 (5.0%)	2 (5.0%)/0 (0.0%)	7 (7.0%)/3 (3.0%)
Angina pectoris	4 (6.7%)	3 (7.5%)	7 (7.0%)
Atherosclerosis of the aorta or brachiocephalic arteries	3 (5.0%)/4 (6.7%)	2 (5.0%)/2 (5.0%)	5 (5.0%)/6 (6.0%)
Atherosclerosis of peripheral arteries	2 (3.3%)	1 (2.5%)	3 (3.0%)
Chronic kidney disease/nephrolithiasis	0 (0.0%)/1 (1.7%)	1 (2.5%)/ 0 (0%)	1 (1.0%)/1 (1.0%)
Diabetic nephropathy	0 (0%)	1 (2.5%)	1 (1.0%)
Proteinuria	0 (0%)	1 (2.5%)	1 (1.0%)
Myocardial ischemia	1 (1.7%)	0 (0%)	1 (1.0%)
Ablation in medical history	1 (1.7%)	0 (0%)	1 (1.0%)

No. – number of patients

Table 2: Concomitant diseases in the patients at baseline.

At the time of inclusion in the trial, 83 patients (83%) had received previous antihypertensive therapy, with ARBs and angiotensin-converting enzyme inhibitors (ACEis) most often used as monotherapy (16.8% and 8.4%, respectively). As many as 58 patients (70%) received a double antihypertensive therapy, with only 25.8% given as SPCs. Among patients receiving combination therapy, 24 patients (29%) were receiving ARBs in combination with CCBs or a diuretic, and 19 patients (22.9%) were receiving ACEis in combination with CCBs or a diuretic (Table 3).

	Grade 2 hypertension group	Grade 3 hypertension group	All patients
No.	60	40	100
Naïve	13	4	17
Previous antihypertensive therapy, No. (%)	47 (78.0%)	36 (90.0%)	83 (83.0%)
Monotherapy, No. (%)	16 (34.0%)	9 (25.0%)	25 (30.0%)
ARB, No. (%)	10 (21.2%)	4 (11.1%)	14 (16.8%)
ACEi, No, (%)	3 (6.4%)	4 (11.1%)	7 (8.4%)
CCB, No. (%)	2 (4.3%)	1 (2.8%)	3 (3.6%)
Beta-blockers, No. (%)	1 (2.1%)	0 (0.0%)	1 (1.2%)
Combinations, No. (%)	31 (66.0%)	27 (75.0%)	58 (70.0%)
ACEi/diuretics, No. (%)	8 (17.0%)	4 (11.1%)	12 (14.5%)
ACEi/CCBs, No. (%)	3 (6.4%)	4 (11.1%)	7 (8.4%)
ARB/diuretics, No. (%)	6 (12.8%)	5 (13.9%)	11 (13.3%)
ARB/CCBs, No. (%)	5 (10.6%)	8 (22.2%)	13 (15.7%)
Other, No. (%)	9 (19.2%)	6 (16.7%)	15 (18.1%)

No. – number of patients

Table 3: Previous antihypertensive therapy at baseline.

Efficacy on the blood pressure reduction

The achievement of the office BP target levels, according to the 2013 ESH/ESC Guidelines for the management of arterial hypertension (SBP < 140 mmHg, DBP < 90 mmHg except in patients with diabetes < 85 mmHg) valid at the time of the trial conduct, were reached by 90% of the patients after 16 weeks of therapy [95% CI 81.2%; 95.6%] (Figure 3). The average reduction in office BP was 32.2 mmHg for SBP and 16.0 mmHg for DBP (Figure 4).

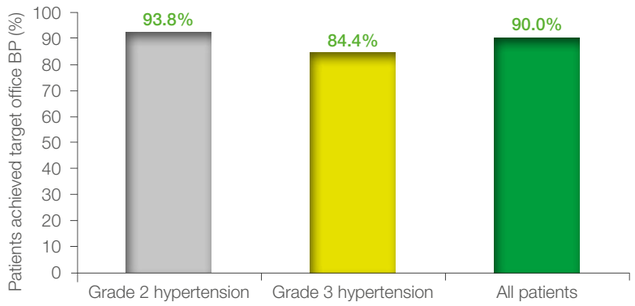


Figure 3: Achievement of the target office BP (BP < 140 mmHg, DBP < 90 mmHg, in the patients with diabetes < 85 mmHg) in all the patients.

In the patients with grade 2 hypertension, the target office BP was reached in 93.8% of the patients; the average reduction in SBP was 30.7 mmHg and 15.5 mmHg in DBP. In the patients with grade 3 hypertension, the target office BP was achieved in 84.4% of the patients; the average reduction in SBP was 34.6 mmHg and 16.7 mmHg in DBP (Figures 3 and 4).

All average changes in office BP at all visits after the start of therapy and in both treatment groups, as well as in all analysed data sets, were highly significant (paired Student t-test, p < 0.001).

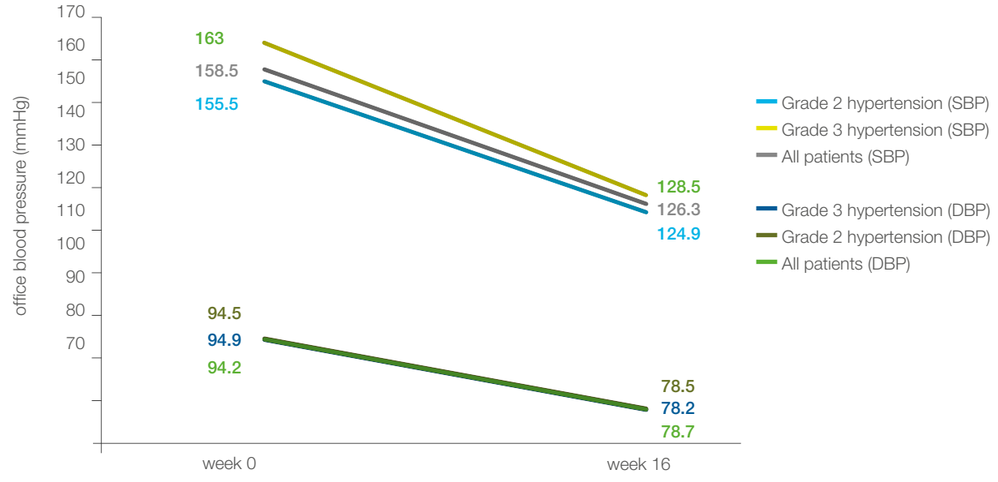


Figure 4: Office SBP and DBP during therapy with amlodipine/valsartan-based SPC therapy.

The proportion of the patients who reached the target BP levels (SBP/DBP < 135/85 mmHg) according to HBPM after 16 weeks of therapy was 40.2% in all the patients [95% CI 30.1%; 51.0%], 32.1% [95% CI 20.3%; 46.0%] in the group with grade 2 hypertension, and 52.8% [95% CI 35.5%; 69.6%] in the group with grade 3 hypertension.

In the subgroup of the patients, with additional 24h ABPM, the average daily SBP/DBP significantly decreased by 11.0/9.5 mmHg after 16 weeks of treatment (Table 4). All 24h ABPM parameters in all the patients and in the group with grade 3 hypertension decreased significantly. In the grade 2 hypertension group, all parameters significantly improved, with the exception of the average nighttime SBP (Table 4).

Parameter		Grade 2 hypertension group			Grade 3 hypertension group			All patients		
		Visit 1 (No. = 27)	Visit 5 (No. = 23)	Percentage of patients achieving target BP	Visit 1 (No. = 13)	Visit 5 (No. = 11)	Percentage of patients achieving target BP	Visit 1 (No. = 40)	Visit 5 (No. = 34)	Percentage of patients achieving target BP
Average daytime (mmHg), (SD)	SBP	136.4 (13.1)	128.5 (13.3)	69.6%	158.8 (22.2)	140.0 (18.8)	45.5%	143.7 (19.4)	132.2 (15.9)	61.8%
	DBP	84.7 (10.3)	76.7 (8.4)	82.6%	94.2 (12.2)	80.7 (6.9)	72.9%	87.8 (11.7)	78.0 (8.1)	79.4%
Average night-time (mmHg), (SD)	SBP	121.9 (14.7)	119.7 (17.6)	52.2%	145.5 (24.3)	128.1 (19.3)	45.5%	129.6 (21.2)	122.4 (18.3)	50.0%
	DBP	72.9 (10.8)	68.6 (9.4)	43.5%	82.7 (11.4)	75.1 (11.4)	36.4%	76.1 (11.8)	70.7 (10.4)	41.2%
Average daily (mmHg), (SD)	SBP	131.5 (12.2)	125.7 (14.6)	56.5%	154.5 (22.5)	136.4 (19.3)	45.5%	134.0 (19.4)	129.2 (16.7)	52.9%
	DBP	80.7 (9.5)	73.8 (8.1)	73.9%	90.8 (11.8)	78.5 (7.2)	54.5%	84.0 (11.2)	75.3 (8)	67.6%

SD – standard deviation, No. – number of patients

Table 4: Dynamics of 24h ABPM parameters and percentage of patients who achieved the target BP during amlodipine/valsartan-based SPC therapy in the patients from the subgroup with additional examinations.

After 16 weeks of therapy, 26.5% of the patients reached the target level of all indicators of the daily BP profile according to the 24h ABPM. Nevertheless, BP reductions according to 24h ABPM after 16 weeks of therapy showed that target levels of mean daily SBP and DBP were reached by 52.9% and 67.6%, respectively, in the subgroup of patients (Table 4).

Effect on central blood pressure

A minimum improvement of 5% in central (aortic) systolic BP was observed in 73% of all the patients from the subgroup with additional examination (38 patients). Central (aortic) SBP was reduced by 16.1 mmHg, from 138.3 to 122.2 mmHg (Table 5). Separately, in groups with grade 2 and 3 hypertension, the 5% improvement of central (aortic) SBP was achieved in 66.7% and 90% of the patients, respectively. The biggest reduction (from 147.4 to 122.7 mmHg) in central (aortic) SBP was seen in the group of the patients with grade 3 hypertension (Table 5).

Parameter	Grade 2 hypertension group		Grade 3 hypertension group		All patients	
	Visit 1	Visit 5	Visit 1	Visit 5	Visit 1	Visit 5
Central aortic systolic pressure (mmHg) mean (SD)	134.6 (15.29) (No. = 27)	122.0 (11.03) (No. = 27)	147.4 (16.94) (No. = 11)	122.7 (12.44) (No. = 11)	138.3 (16.62) (No. = 38)	122.2 (11.29) (No. = 38)
PWV (m/s), mean (SD)	10.37 (2.69) (No. = 26)	9.92 (2.94) (No. = 25)	11.05 (2.76) (No. = 11)	10.25 (3.05) (No. = 11)	10.57 (2.69) (No. = 37)	10.02 (2.93) (No. = 36)

SD – standard deviation; No. – number of patients

Table 5: Changes in central (aortic) systolic pressure and in PWV in a subgroup of patients with additional examinations.

Effect on vessel function

When evaluating the effect of amlodipine/valsartan-based SPC therapy on arterial elasticity in the subgroup of patients with additional examinations, improvement in PWV of at least 5% was observed in 57.1% of the patients, 48% and 80% in the groups with grades 2 and 3 hypertension, respectively.

In the group of the patients with grade 2 hypertension, a reduction of PWV from 10.37 m/s at baseline to 9.92 m/s after 16 weeks of treatment was observed (Figure 5).

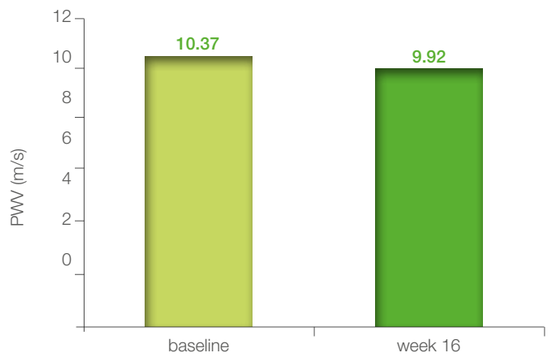


Figure 5: PWV (m/s) during treatment with amlodipine/valsartan-based SPCs in a subgroup of patients with grade 2 hypertension with additional examinations.

An improvement in the augmentation index by ≥ 5% was observed in 66.7% of the patients; 61.5% and 80% in the groups with grades 2 and 3 hypertension, respectively. The largest decrease was observed in the group with grade 2 hypertension. The combined improvement in PWV and the augmentation index of ≥ 5% was observed in 44.1% of the subgroup patients and in 33.3% and 70% in the groups with grades 2 and 3 hypertension, respectively.

The levels of parameters involved in endothelial damage (IL-6, IL-10, TNFα, sVCAM, VEGF-A) were assessed before the administration of the amlodipine/valsartan-based therapy and after 16 weeks of treatment (Table 6). Intra-group absolute changes of these parameters were statistically significant at the 5% level of change in values for IL-6, IL-10, VEGF-A, TNFα, except for sVCAM-1, in the subgroup of 38 patients after 16 weeks of treatment (Visit 5).

Parameter	Grade 2 hypertension group		Grade 3 hypertension group		All patients	
	Visit 1 (No. = 27)	Visit 5 (No. = 27)	Visit 1 (No. = 12)	Visit 5 (No. = 11)	Visit 1 (No. = 39)	Visit 5 (No. = 38)
IL-6, median	1.26	1.39	1.17	1.46	1.25	1.42
IL-10, median	0.42	0.09	0.49	0.19	0.44	0.10
sVCAM-1, median	655.80	723.30	679.65	547.70	669.30	586.50
VEGF-A, median	79.40	57.35	87.38	63.73	79.40	57.88
TNFα, median	0.25	0.68	0.39	1.14	0.25	0.70

Table 6: Median values of endothelium function parameters in a subgroup of patients with additional examinations.

Relative decrease in values of IL-10 levels by a minimum of 5–15% was observed in 76.3% of the patients. A decrease in the level of the vascular endothelial adhesion molecule (sVCAM-1) by a minimum of 5% was observed in 47.4% of the patients. A decrease in TNFα levels by a minimum of 5–10% was observed in 10.5% of the patients. A decrease in the level of the vascular endothelial growth factor (VEGF-A) molecule by a minimum of 5%, 10% and 15% was observed in 68.4%, 63.2%, and 60.5% of the patients, respectively.

Effect on kidney function

Initially elevated level of albumin (≥ 30 mg/day) was detected in 17 patients. The changes in the albumin are presented in Table 7.

Parameter	Grade 2 hypertension group		Grade 3 hypertension group		All patients	
	Screening visit (No. = 58)	Visit 5 (No. = 56)	Screening visit (No. = 37)	Visit 5 (No. = 36)	Screening visit (No. = 95)	Visit 5 (No. = 92)
Albumin median [min; max]	10.0 [0; 230.0]	8.0 [0; 200.0]	7.0 [0; 272.0]	4.6 [0; 2867.0]	9.0 [0; 272.0]	7.13 [0; 2867.0]

No. – number of patients

Table 7: Changes of albumin levels in urine, median, minimum and maximum.

During the observation, a positive effect of the studied medication (the amount of albumin in the urine per day became less than 30 mg) was found in 58.8% (10 patients) of the patients after 16 weeks of treatment. The transition from gradient ≥ 30 mg/day at the screening visit to gradient less

than 30 mg/day at Visit 5 was observed in 60.0% and 57.1% of the patients in the grade 2 and 3 hypertension groups, respectively.

Effect of the treatment on metabolic parameters

The treatment with amlodipine/valsartan and amlodipine/valsartan/HCTZ SPCs was not associated with changes of the metabolic parameters related to a CV disease. The mean initial blood glucose values, total cholesterol, LDL cholesterol, HDL-cholesterol, triglycerides, and uric acid did not change in 90.7%, 79.6%, 81.1%, 90.6%, 83.3% and 88.0% of the patients, respectively. All these parameters were checked in all the patients.

Effect of the treatment on erectile function

The effect of amlodipine/valsartan-based SPC on erectile function in all the male patients was assessed by use of self-evaluation with IIEF-5 questionnaires by male patients. Questionnaires were filled in by the patients included in the trial, at the beginning (Visit 1) and at the end of the trial (Visit 5). For all 39 male patients included in the analysis, the average change in the indicator (improvement) was statistically significant ($p = 0.048$). As many as 51.3% of all the hypertensive male patents included in the trial reported a positive effect of the amlodipine/valsartan-based treatment on erectile function.

Effect of the treatment on quality of life and convenience of the therapy

As many as 98 patients filled out the SF-36 questionnaire at Visit 1 and after 16 weeks of treatment with the tested medicines. Since there is no generally accepted validated definition in what cases (according to the SF-36 questionnaire) the patient´s quality of life changed positively, a calculation was made of the average values on the scales for visits, as well as the corresponding average changes compared to the initial values. The change in the quality of life in numerical terms is presented in Table 8. In all parameters, except the physical functioning, the positive change was statistically significant.

Parameters	Average change	95% confidence interval (P-value)
Pain	8.9	4.4%–13.4% (0.017)
Vitality	6.4	3.1%–9.7% (< 0.001)
General health	5.8	2.5%–9.1% (0.001)
Mental Health	5.5	2.3%–8.7% (0.001)
Role playing	10.2	2.9%–17.5% (0.007)
Social Functioning	9.9	6.1%–13.7% (< 0.001)
Physical Functioning	1.5	-1.6%–4.5% (0.339)
Emotional Functioning	12.6	5.0%–20.1% (0.001)

Table 8: Change in the quality of life after 16 weeks of treatment with amlodipine/valsartan-based SPC, based on the results of the filled-out questionnaire for assessing the quality of life (SF-36) in all the patients.

Based on the visual analogue scales questionnaire, 50.0% of the patients (38 out of 76 patients), i.e. 47.8% (22 patients) and 53.3% (16 patients) in groups with grades 2 and 3 hypertension, respectively, self-reported the studied medicines as more convenient compared to their previous antihypertensive therapy. Among the factors indicating the convenience of antihypertensive therapy, a positive dynamics was observed for the following: the possibility to lead normal life, pill burden, frequency of administration, and efficacy of the treatment (Table 9).

Parameter	Grade 2 hypertension group		Grade 3 hypertension group		All patients	
	Visit 1 (No. = 46)	Visit 5 (No.= 60)	Visit 1 (No. = 31)	Visit 5 (No. = 38)	Visit 1 (No. = 77)	Visit 5 (No. = 98)
Possibility to lead normal life	21 (45.6%)	30 (50.0%)	17 (54.8%)	22 (57.9%)	38 (49.4%)	52 (53.1%)
Number of tablets taken at the same time (pill burden)	18 (39.1%)	31 (61.7%)	15 (48.4%)	28 (73.7%)	33 (42.9%)	65 (66.3%)
Frequency of administration	27 (58.7%)	44 (73.3%)	16 (51.6%)	33 (86.8%)	44 (52.1%)	77 (78.6%)
Efficacy of the treatment	29 (63.0%)	37 (61.7%)	19 (61.3%)	27 (71.1%)	48 (62.3%)	64 (65.3%)

No. – number of patients

Table 9: Convenience factors of current therapy from patients' point of view.

Safety of the treatment

The trial data indicated good tolerability of amlodipine/valsartan SPC-based treatment. AEs associated with the administration of the tested medicines included orthostatic hypotension (10%), peripheral oedema (7%), headache (1%), dizziness (1%), asthenia (2%), and hypotension (2%). Only six AEs in five patients (5%) led to the discontinuation of the trial therapy. These were peripheral oedema (3 cases), atrial fibrillation and pneumonia, and allergic dermatitis. Three AEs in two patients (2%) were considered serious and only one was associated with taking the tested medicines. There were no deaths during the trial period.

Overall therapeutic efficacy

The therapeutic effect of the treatment was assessed in all the patients at the end of the trial after 16 weeks of treatment. The overall clinical efficacy, evaluated as extremely high, very high, high, and satisfactory, was achieved in 98.8% [95% CI 93.2%; 100 %] of the patients.

Discussion

The data of the VICTORY II clinical trial showed that the amlodipine/valsartan-based treatment is effective in reducing BP to the target levels in newly diagnosed or previously treated, but uncontrolled patients with grade 2 or 3 arterial hypertension. The initiation of the therapy or switching to amlodipine/valsartan-based SPC therapy resulted in the achievement of target office BP in 90% of the patients after 16 weeks of therapy. The time needed to achieve the target BP levels is an important determinant of clinical outcomes. Shorter time to control is associated with a lower CV risk. The achieved levels of target office BP were similar in the patients with grade 2 and grade 3 hypertension (124.9/78.8 mmHg and 126.3/78.2 mmHg, respectively). Although the trial was conducted at the time of validity of 2013 *ESH/ESC* Guidelines for the management of arterial hypertension, the levels of BP achieved are in line with the treatment objectives of current guidelines. Namely, the current 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend that the first objective of treatment should be to lower BP to < 140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower (but not lower than 120 mmHg) in most patients.[1]

The design of the trial was ahead of time, since the initiation of the hypertension treatment was based on the SPC of RAASi/CCB. This kind of treatment is now recommended as the first-line

therapy by the current 2018 ESC/ESH Guidelines for the management of arterial hypertension and also by the most recent 2020 ISH guidelines for the management of hypertension. The results of the clinical trial comply with both current guidelines and show that the initial treatment of hypertension with the double SPC and upgrade to the triple SPC is more efficient than monotherapy.

The current valid 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend HBPM for the diagnosis and follow-up of hypertension.[1] According to HBPM in the presented trial, 40.2% of the patients reached the target BP levels (SBP/DBP < 135/85 mmHg) after 16 weeks of therapy. Achievement of target HBPM levels was determined based on a strict criterion, i.e. absence of cases of exceeding the target BP levels during the last seven days of the administration of the medicine before the final visit at week 16. When analysing these results, it is important to take into account that the HBPM assessment can be problematic if the technology for measuring/recording the results and patient compliance with the received instructions for BP measuring are not carefully defined. Adherence to HBPM guidelines despite a passive, multimodal intervention is still suboptimal, indicating low reliability of the data.[12] The accuracy and reproducibility of data when using BP measuring devices with a memory function was shown to be much higher compared to the use of HBPM diaries.[13] Maintaining a satisfactory quality of HBPM diary may also be insufficient, as it is also bringing a diary to the physician.[12] HBPM measurements may also be affected by the patients' lifestyle: their eating habits, fluid balance, emotional background, alcohol intake, etc.[14] The trial identified the assessment of HBPM, along with the proper quality of BP measurements by patients at home, as challenging.[13] Considering the limitations in evaluation of the trial results, this practice needs further investigation. Nevertheless, the active involvement of patients to perform HBPM and keep a measurement diary, and encouraging them to share it with the physician via telemedicine is nowadays, in the time of COVID-19 pandemics with reduced/limited visits of patients to the physician's office, of crucial importance. In accordance with the current situation, the newest 2021 ESH practice guidelines for office and out-of-office BP measurement recommend wider use of out-of-office BP measurement, especially HBPM.[15] A HBPM diary can serve as an effective and practical tool for guiding antihypertensive medication initiation and titration, especially in current times of telemedicine clinical care. [15]

In the trial, 24h ABPM was used to assess 24-h BP lowering efficacy of the amlodipine/valsartan-based SPC therapy in the subgroup of patients. 24h ABPM improves the accuracy of diagnosis of hypertension and detects patients with uncontrolled masked hypertension.[1] Due to white coat hypertension, the office BP may be substantially higher than BP during normal daily activities in many individuals. This may lead to incorrect diagnosis of hypertension in untreated individuals.[3] The average BP values recorded by 24h ABPM are lower than the office BP readings, which results in smaller reduction of BP during treatment. In the VICTORY II trial, 26.5% of the patients treated with amlodipine/valsartan-based SPC normalised BP according to 24h ABPM measurements. Nevertheless, all average changes of BP were statistically significant at a significance level of 5%, with the exception of the average night-time SBP in the group of patients with grade 2 hypertension ($p = 0.364$) and average night-time DBP in the group of patients with grade 3 hypertension ($p = 0.086$). The amlodipine/valsartan-based SPC therapy improved daily BP profile of the patients with grade 2 and 3 hypertension, indicating additional positive effect on patients' prognosis.

Meta-analyses have shown that, in hypertensive patients, central BP is a better predictor of CV events compared to brachial BP.[16] There is also a different effect of antihypertensive medicines on central BP compared with brachial BP.[2] The reduction of central BP also decreases CV risk and HMOD.[4] The treatment with amlodipine/valsartan-based SPCs showed a significant reduction of central (aortic) BP in almost three quarters of the patients. Interestingly, similar data were obtained in the international multicentre clinical trial VICTORY in which valsartan and the SPC of valsartan/HCTZ significantly reduced the stiffness of the aorta and, consequently, PWV and central BP in 74% of the patients with grade 1 and grade 2 hypertension.[17]

Many patients included in the VICTORY II trial had concomitant conditions that affect the progression of the CVD. Therefore, the choice of antihypertensive treatment, which has a beneficial effect on slowing the progression of CVD, is of great importance. Increased BP and neurohumoral dysregulation are likely to have an adverse effect on the kidneys. Reduction of albuminuria, as an early marker of kidney disease, translates into a decreased occurrence of CV and renal outcomes.[18] It is well established that ARBs (e.g. valsartan), exert renoprotective effects beyond their BP-lowering effects due to the benefits on renal injury during the development of hypertension. Furthermore, ARB-induced renal vasodilation results in an increase in renal blood flow, leading to an improvement of renal ischemia and hypoxia. ARB is effective in reducing the urinary albumin excretion rate independently of BP reduction.[19] It has been shown that the treatment strategy, which includes an ACEi or ARB, decreased albuminuria and the appearance or progression of diabetic nephropathy more effectively than other medicine classes.[1] The decrease of albuminuria by amlodipine/valsartan-based SPC therapy was also seen in the VICTORY II clinical trial. In more than half of the included patients with initial albuminuria there was an improvement of albuminuria and, consequently, improved kidney function.

In patients with hypertension, increased BP can increase arterial stiffness. In the 2018 ESC/ESH Guidelines for the management of arterial hypertension, carotid-femoral PWV is the gold standard for measuring large artery stiffness. A PWV >10m/s is considered a conservative estimate of significant alterations of the aortic function in middle-aged hypertensive patients.[1] Significant evidence suggests that the increase in arterial stiffness is an independent risk factor for CV diseases.[20] An ideal antihypertensive medicine should, therefore, lower BP and improve arterial stiffness.[2] By reducing BP, all antihypertensive medicines also reduce arterial stiffness.[1] Meta-analyses of many randomised clinical trials suggest that ACE inhibitors and ARBs may reduce PWV beyond the effect of BP-lowering on a long-term basis.[1, 20] The positive effect of amlodipine/valsartan-based SPC therapy was also seen in the VICTORY II clinical trial. In the group of patients with additional examination, two out of three patients treated with an SPC based on amlodipine/valsartan exerted at least a 5% drop in PWV, leading to mean PWV of 10 m/s after 16 weeks of treatment. This showed a positive marked effect of the treatment on arterial elasticity. The beneficial effect of the amlodipine/valsartan-based SPC therapy on arterial stiffness can be explained by a potential impact of valsartan and amlodipine included in the SPC on the vascular wall. Valsartan, by blocking the RAAS, suppresses proinflammatory angiotensin II signals and reduces the severity of oxidative stress. It promotes normalisation of the endothelium and ensures proper vasodilatation, which slows down remodelling and connective tissue restructuring of the vascular wall.[21] CCBs can block N-calcium channels at the endings of sympathetic nerves, which has a local sympatholytic effect through a suppression of adrenergic effects on blood vessels. A decrease in the basal tone of smooth muscle cells and inhibition of the tonic component contribute to a decrease in the rigidity of the arterial wall.[22]

Atherosclerosis is primarily a disorder of lipid metabolism; however, there is also a prominent chronic inflammatory component that drives the atherosclerotic lesion progression in the artery wall.[23] The accumulation of inflammatory cells within the arterial wall leads to a local production of inflammatory markers, such as interleukins (e.g. IL-6, IL-10), cytokines, and proteases. They enhance the influx of monocytes and lymphocytes, thereby promoting the progression of atherosclerotic lesions.[24] The vascular endothelial growth factor (VEGF) is an important angiogenic factor. It induces migration and proliferation of endothelial cells, enhances vascular permeability, and modulates thrombogenicity. Macrophage recruitment by abnormal endothelium in developing atherosclerotic plaques is aided by the endothelial expression of adhesion molecules (e.g. vascular cell adhesion molecule (VCAM)).[25] Antihypertensives as antiinflammatory agents can play a key role in atherosclerotic lesions. Previous investigations revealed that valsartan might inhibit the development of atherosclerosis by lowering serum pro-inflammatory cytokines.[26] In the VICTORY II

clinical trial, the effect of amlodipine/valsartan-based SPCs on inflammatory parameters was also evaluated. The levels of the vascular endothelial growth factor A (VEGF-A), a key regulator of angiogenesis, significantly decreased in all the patients of the subgroup with additional examinations, including the group of patients with grade 3 hypertension. The obtained data on the effect of amlodipine/valsartan-based SPCs on inflammatory parameters require further investigation since multidirectional changes were detected among the many parameters.

Limitations of the trial

The design features of this trial are close to real clinical practice: open design, lack of randomisation of patients and control groups not allowing for a comparison of SPC's effects on the tested parameters with other treatments (e.g. each component of SPC). In addition, strict criteria for achieving the target HBPM levels, not carefully defined compliance with the received instructions for HBPM and, therefore, poor quality of BP measurements by patients lead to lower achievement of target HBPM values.

Conclusion

The results of the VICTORY II clinical trial showed that amlodipine/valsartan-based SPC therapy effectively reduced BP in patients with grade 2 or 3 hypertension. High rates of achieved office BP target levels were provided in a short 16-week period. The therapy also provided a broad spectrum of clinical benefits beyond BP control, such as positive impact on elasticity of the vessel and endothelial function, improvement of kidney function through reduction of albuminuria with a good safety profile during the entire follow-up period. Moreover, the studied medicines were evaluated by the patients as more convenient in comparison to the previous treatment, showing positive impact on erectile function in men and improvement of the general quality of life in all the patients. The results of the VICTORY II clinical trial demonstrate that amlodipine/valsartan-based SPC therapy in patients with grade 2 and 3 hypertension is an effective and safe treatment strategy, which fully complies with the current guidelines for hypertension treatment.

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