Kardiologia Polska 2018; 76, 2: 328–337; DOI: 10.5603/KP.a2017.0240

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The efficacy and safety of valsartan and a combination of valsartan and hydrochlorothiazide in the treatment of patients with mild to moderate arterial hypertension: a subgroup analysis of the effect of valsartan and its combination with hydrochlorothiazide on pulse wave velocity and central blood pressure

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Abstract

Background and aim: The aim of the study was to establish the effect of valsartan and combination of valsartan and hydrochlorothiazide (HCTZ) on pulse wave velocity (PWV) and central blood pressure (CBP) in a large population of patients with mild to moderate arterial hypertension.

Methods: This was an international, multicentre, open-label, prospective trial. After one week of washout in previously treated patients, 74 subjects were treated with valsartan or valsartan combined with HCTZ for 16 weeks according to the protocol. Naïve patients received the treatment immediately. During the active treatment, four visits were planned for each patient to obtain data for the primary and secondary efficacy. At the beginning and at the end of the study PWV and CBP were determined with central arterial pressure waveform analysis (SphygmoCor®, Atcor Medical). This study is registered with clinicaltrialsregister.eu, EudraCT number 2012-005129-57.

Results: The results of the present VICTORY trial showed that valsartan and combination of valsartan and HCTZ effectively reduced the brachial blood pressure in patients with mild to moderate arterial hypertension as well as PWV, central systolic blood pressure and central diastolic blood pressure. The effects on the augmentation index were not statistically significant.

Conclusions: Valsartan and valsartan/HCTZ improve arterial stiffness in patients with mild to moderate hypertension.

Key words: pulse wave analysis, antihypertensive agent, valsartan, clinical trial

Kardiol Pol 2018; 76, 2: 328–337

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Received: 15.11.2017 **Accepted:** 23.11.2017 **Available as AoP:** 30.11.2017

INTRODUCTION

Arterial hypertension is one of the most important risk factors for cardiovascular morbidity and mortality. It is defined as blood pressure (BP) persistently at or above 140/90 mmHg [1, 2]. Pharmacological treatment is necessary in most patients even with mild to moderate hypertension in spite of lifestyle changes [3, 4].

Angiotensin receptor blockers (ARBs) or sartans (e.g. valsartan) are among first line medications for hypertension treatment. They can be used either alone or in combinations with other antihypertensive agents (e.g. hydrochlorothiazide [HCTZ]).

Recent epidemiologic studies have shown that, independently of confounding factors such as age, BP and cardiac mass, aortic pulse wave velocity (PVW) is a predictor of cardiovascular mortality in populations of hypertensive subjects, whether they have end-stage renal disease or not [5].

Emerging evidence now suggests that central pressure is better related to future cardiovascular events than brachial pressure. Moreover, antihypertensive drugs can exert differential effects on brachial and central pressure. Therefore, basing treatment decisions on central, rather than brachial pressure is likely to have important implications for the future diagnosis and management of hypertension [6–8].

The aim of the trial was to establish the efficacy on central blood pressure (CBP) and aortic stiffness of valsartan and fixed-dose combination of valsartan and HCTZ in wide populations of patients with mild to moderate arterial hypertension.

METHODS

Investigational plan

The present trial was designed as an international, multicentre, open-label, prospective, phase IV trial, performed in five countries: Slovenia (seven clinical centres), Czech Republic (three clinical centres), Croatia (three clinical centres), Ukraine (three clinical centres) and Russian Federation (nine clinical centres).

Inclusion and exclusion criteria

Inclusion criteria:

Patients of both genders with mild to moderate essential hypertension (according to the 2009 European guidelines for the management of arterial hypertension) with:

- systolic blood pressure (SBP) of 140–179 mmHg and
- diastolic blood pressure (DBP) of 90–109 mmHg;
- age 18 years or above;
- written informed consent provided by patients or legally acceptable representative.

Exclusion criteria:

- Blood pressure values 180/110 mmHg or higher during washout period (hypertensive crisis),
- Secondary hypertension (due to renovascular hypertension, endocrine disorders [pheochromocytoma, primary hyperaldosteronism, Cushing's syndrome, acromegaly]), malignant hypertension, treatment-resistant hypertension,
- Hypovolemia due to salt-restricted diet, dialysis, diarrhoea or vomiting,
- Haemodynamically significant aortic stenosis or bilateral stenosis of the renal artery or arterial stenosis of a solitary kidney,
- History of angioedema (hereditary, idiopathic or related to previous treatment),
- Hypertensive encephalopathy,
- Angina pectoris or heart failure requiring treatment with a beta-blocker or a calcium antagonist or cardiovascular event (unstable angina pectoris, myocardial infarction, transient ischaemic attack or stroke or cerebrovascular insult) within the preceding three months,
- Acute liver disease or hepatic dysfunction and other acute diseases (infection, acute exacerbation of chronic diseases, trauma, surgical intervention) within the period of the past three months,
- Renal failure (creatinine clearance < 60 mL/min) or clinically significant abnormal concentrations of serum creatinine or potassium,
- Diabetes mellitus treated with insulin or uncontrolled diabetes mellitus with fasting blood glucose greater than 11 mmol/L,
- Concomitant treatment that might influence the final therapeutic effect of the tested active substances,
- Pathological clinical states that could affect patient's compliance, or have any impact on the patient's survival (malignant diseases, alcohol abuse, drug addiction, psychiatric diseases),
- Hypersensitivity to any of the tested medicines,
- Participation in another clinical trial within 30 days prior to enrolment,
- Patients who are not able out of any reason to fulfil the requirements of the protocol.

Patients could withdraw from the trial after being included, if they wanted to discontinue the treatment and then withdraw (patient's dropouts). The study was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, the International Conference on Harmonisation's Harmonised Tripartite Guidelines for Good Clinical Practice, and applicable regulatory requirements. The study protocols were reviewed by independent ethics committees or institutional review boards and all patients provided written informed consent before entering the studies.

The duration of the active treatment was 16 weeks [9]. The trial was financially supported by KRKA d. d., Novo mesto, Slovenia.

We tested valsartan 80 mg, valsartan 160 mg, valsartan 320 mg and valsartan 160 mg/HCTZ 12.5 mg, valsartan

Table 1. Parameters assessed during the trial

Parameter	At visit 1 (washout — only for previously treated patients)	At visit 1 (start of active treatment for all eligible patients)	At visit 5 (last control visit: end of the trial)
Body height		x	x
Body weight		x	x
Systolic BP	x	x	x
Diastolic BP	x	x	x
Heart rate	x	x	x
PWV and central BP		x	x

BP — blood pressure; PWV — pulse wave velocity

320 mg/HCTZ 12.5 mg. Drugs (Valsacor® and Valsaden®/ /Valsacor® H and HD/Valsacombi®) were provided by KRKA d. d., Novo mesto, Slovenia.

Patients took the medication once daily between 7 a.m. and 10 a.m. On the day of the control visit patients did not take the trial drugs before the BP measurement at the visit was performed. The treatment was initiated with one tablet of valsartan 80 mg daily in all patients (naïve and previously treated patients). Only in Russia, previously treated patients at the first visit received valsartan in a dose of 160 mg (request from the ethical committee), which did not have any influence on study results. After four weeks of treatment, the dose was adjusted to one tablet of valsartan 160 mg (in Russia also to one tablet of valsartan 320 mg or valsartan 160 mg/HCTZ 12.5 mg) daily in patients whose BP was not lowered to 140/90 mmHg or 130/80 mmHg or less. After the subsequent four weeks in insufficiently treated patients the dose was increased to valsartan 320 mg or the fixed dose combination of valsartan 160 mg/HCTZ 12.5 mg (in Russia also to one tablet of valsartan 320 mg/HCTZ 12.5 mg). If target BP levels were not achieved after additional four weeks the dose was increased to valsartan 320 mg/HCTZ 12.5 mg.

Besides standard procedures to assess medical history, physical examination, and vital signs assessment, special procedures were applied to assess baseline status of the disease and changes after the therapeutic intervention (Table 1).

BP measurement

Blood pressure was measured at every visit in the morning hours (7 a.m. – 10 a.m.) prior to administration of the morning dose of the tested drug. In each patient, at all visits, BP was measured by a validated oscilometric device and by the same investigator or another member of the authorised medical staff.

During the measurement patient was seating in a chair with the back supported and the arms bared and supported at heart level. Three measurements were performed in at least 2-min intervals and the obtained values were recorded with an accuracy of at least 2 mmHg. The mean of the last two measurements was considered as the final BP value.

At the first visit BP was measured on both arms. At the following visits BP was only measured on the arm which showed higher BP value at the first visit measurement.

Target BP values were defined according to the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of arterial hypertension [10].

PWV and CBP measurements

Pulse wave velocity and CBP measurements were assessed at the visit 1 and visit 5 with a validated central arterial pressure waveform analysis (SphygmoCor®, Atcor). The same analysis was used at both measurements (visit 1 and visit 5) by the same operator and in the same way.

After 5 min of lying down, the same validated oscilometric device was used and BP was measured three times in 1-min intervals. All three values were recorded and the average was used for the measurement of CBP with the central arterial pressure waveform analysis.

Simultaneous electrocardiogram (ECG) recording and capturing pulse waveform on the femoral artery, and then carotid artery with the tonometer were used to measure PWV. By entering/calculating the distance between two sites, PWV was calculated.

Radial artery applanation tonometry and pulse wave analysis was used to capture pulse wave to calculate central BP.

Endpoints

Primary endpoints were to evaluate the effect of treatment on aortic stiffness, the effect of treatment on aortic augmentation index (AIx) and to compare the absolute (mean) differences in CBP reduction versus peripheral BP reduction versus baseline values.

Secondary endpoints were to compare primary endpoints between the monotherapy versus combination therapy.

Statistical analysis

The data was presented as follows: the largest and the smallest values, arithmetic mean with standard deviation or standard error of mean and the t variable in the t-test. For ratio scale

Table 2. Characteristics of the patients

	PWV subgroup (n = 74)		Monotherapy from PWV subgroup (n = 59)		Combination therapy from PWV subgroup (n = 15)	
	Mean or proportion	CI for mean or proportion	Mean or proportion	CI for mean or proportion	Mean or proportion	CI for mean or proportion
Age [year]	50.54	(47.40, 53.69)	49.86	(46.57, 53.16)	53.20	(50.74, 55.66)
Sex (males)	37 (50%)	(38%, 62%)	29 (49%)	(36%, 63%)	8 (53%)	(27%, 79%)
Smoker:	16 (22%)	(13%, 33%)	12 (20%)	(11%, 33%)	4 (27%)	(8%, 55%)
Regular smoker	8 (11%)	(5%, 20%)	6 (10%)	(4%, 21%)	2 (13%)	(2%, 40%)
Occasional smoker	1 (1%)	(0%, 7%)	1 (2%)	(0%, 9%)	0 (0%)	(0%, 22%)
Ex-smoker	7 (9%)	(4%, 19%)	5 (8%)	(3%, 19%)	2 (13%)	(2%, 40%)
Alcohol:	36 (49%)	(37%, 61%)	30 (51%)	(27%, 64%)	6 (40%)	(16%, 68%)
Regular consumption	1 (1%)	(0%, 7%)	1 (2%)	(0%, 9%)	0 (0%)	(38%, 62%)
Occasional consumption	25 (34%)	(23%, 46%)	21 (36%)	(24%, 49%)	4 (27%)	(8%, 55%)
Other	10 (14%)	(7%, 23%)	8 (14%)	(6%, 25%)	2 (13%)	(2%, 40%)
Systolic BP [mmHg]	154.69	(152.72, 156.66)	153.45	(151.49, 155.40)	159.60	(154.20, 165.00)
Diastolic BP [mmHg]	95.78	(94.47, 97.09)	95.24	(93.75, 96.73)	97.93	(95.42, 100.45)
Heart rate [bpm]	70.81	(68.93, 72.69)	70.08	(68.12, 72.05)	73.67	(68.68, 78.66)
Height [cm]	171.95	(169.59, 174.31)	171.15	(168.61, 173.69)	175.07	(169.18, 180.96)
Weight [kg]	87.77	(83.80, 91.75)	85.45	(81.79, 89.11)	96.91	(84.29, 109.52)
Chronic heart failure	6 (8%)	(3%, 17%)	4 (7%)	(2%, 16%)	2 (13%)	(2%, 40%)
Peripheral artery disease	1 (1%)	(0%, 7%)	1 (2%)	(0%, 9%)	0 (0%)	(0%, 22%)
Renal disease	9 (12%)	(6%, 22%)	7 (12%)	(5%, 23%)	2 (13%)	(2%, 40%)
Diabetes type 2	5 (7%)	(2%, 15%)	4 (7%)	(2%, 16%)	1 (7%)	(0%, 32%)
Hyperlipidaemia	35 (47%)	(36%, 59%)	29 (49%)	(36%, 63%)	6 (40%)	(16%, 68%)
Hypercholesterolaemia	40 (54%)	(42%, 66%)	33 (56%)	(42%, 69%)	7 (47%)	(21%, 73%)
Hypertriglyceridaemia	13 (18%)	(10%, 28%)	11 (19%)	(10%, 31%)	2 (13%)	(2%, 40%)

BP — blood pressure; CI — confidence interval; PWV — pulse wave velocity

variables, the mean and the asymptotic confidence interval (CI) for the mean are given. For dichotomous variables, the total count, the proportion and the Clopper-Pearson 95% CI are given. The unpaired two-tailed Student's t-test and 95% CI was used to compare values between the treatment groups. Differences were considered to be significant at $p < 0.05$.

RESULTS

Study patients

There were 365 patients included in the VICTORY trial [9]. Ninety (from the 140 planned subjects) were included in the PWV and CBP subgroup. At the end of the trial, 74 were included in the subgroup. The reasons for the patient's withdrawal was either noncompliance (three or more missed consecutive doses, or 20% or more missed doses in a trial period [i.e. between visit 2 and visit 3]), or missed visits (more than one).

Only patients with all PWV parameters are included to the PWV subgroup. Patients are divided into the monotherapy and combination therapy subgroups, which they had been receiving in the treatment period. Characteristics of the PWV subgroup are listed in Table 2.

Primary efficacy endpoint — to evaluate the effect of treatment on PWV (ITT analysis)

The results on the first and the last visit showed that mean PWV value at the beginning of the trial was higher than the mean PWV value at the end of the trial and the aortic stiffness was higher at the beginning of the trial.

Table 3 shows the mean PWV values on the first and the last visit of the trial. The mean absolute decrease of PWV from the first to the last visit was 0.95 ± 1.87 m/s and mean relative decrease of PWV was $8.4 \pm 17.6\%$. Taking into account that the degree of freedom for paired t-test was 73, the decrease was statistically significant ($p < 0.0001$).

Figure 1 shows the trend of PWV decrease during the trial. The majority of lines in the graph showed a decrease of PWV.

Table 3. The pulse wave velocity (PWV) values during the trial

Visit	N	Mean PWV		
		Average	SD	Asymptomatic CI
Visit 1	74	10.09	2.50	(9.51, 10.67)
Visit 5	74	9.14	2.56	(8.55, 9.73)

CI — confidence interval; SD — standard deviation

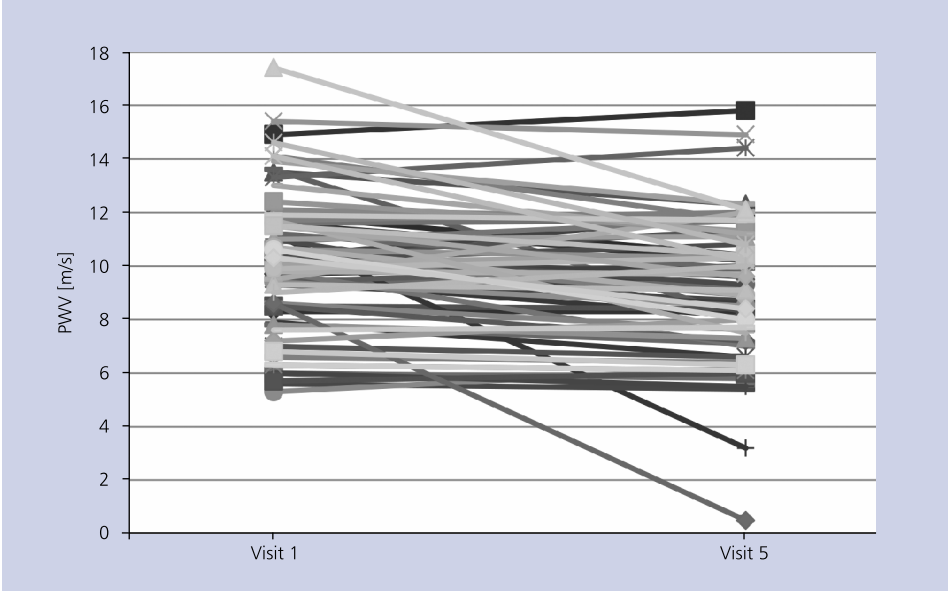

Figure 1. Pulse wave velocity (PWV) values on the first and the last visit for 74 patients from subgroup

Primary efficacy endpoint — to evaluate the effect of treatment on aortic AIx (ITT analysis)

The data on AIx were obtained on the first and the last visit of the trial in a subgroup of patients. 74 patients, from whom the PWV data on the first and the last visit were obtained, were included in the ITT analysis.

Table 4 shows the mean AIx values on the first and the last visit of the trial. The mean absolute decrease of AIx from the first to the last visit was 0.23 ± 10.78. The value of paired t-test for mean AIx reduction from the first to the final visit was 0.18. Taking into account that the degree of freedom for paired t-test was 73, the decrease was statistically insignificant ($p = 0.855$).

Primary efficacy endpoint — to compare the absolute (mean) differences in CBP reduction versus peripheral BP reduction versus baseline values (ITT analysis)

The data on central and peripheral BP were obtained on the first and the last visit of the trial in a subgroup of patients. 74 patients were included in the ITT analysis.

Tables 5 and 6 represent the mean central and peripheral SBP and DBP on the first and the last visit of the trial. The mean absolute decrease of central SBP and DBP were 19.69 ± 12.95 mmHg (mean relative decrease was 13.8 ± 8.6%) and 13.99 ± 8.51 mmHg (mean relative decrease was 14.3 ± 8.5%), respectively. On the other hand, the mean absolute decrease of peripheral SBP and DBP were 20.93 ± 12.79 mmHg (mean relative decrease was 13.6 ± 7.7%) and 13.84 ± 8.69 mmHg (mean relative decrease was 14.3 ± 8.8%), respectively.

The decreases of both central and peripheral mean SBP and DBP between the first and the last visit of the trial were significant ($p < 0.0001$). Taking into account that the degrees of freedom for all paired t-test were 73, the decreases were in all cases statistically significant ($p < 0.0001$).

Figures 2 and 3 clearly showed the trend of CBP decrease during the trial. The majority of lines in both graphs shows decreases of central SBP or DBP.

Secondary efficacy endpoint — to compare primary endpoints between the monotherapy versus combination therapy (PP analysis)

Effect of treatment on aortic stiffness (PP analysis)

The aortic stiffness was improved in both monotherapy and combination therapy group. In both groups, PWV decreased

Table 4. The augmentation index (AIx) values during the trial

		Mean AIx		
Visit	N	Average	SD	Asymptomatic CI
Visit 1	74	19.9	13.4	(16.8, 22.9)
Visit 5	74	19.6	12.3	(16.8, 22.5)

CI — confidence interval; SD — standard deviation

Table 5. Mean central systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the first and the last visit of the trial

		Central SBP [mmHg]			Central DBP [mmHg]		
Visit	N	Average	SD	Asymptomatic CI	Average	SD	Asymptomatic CI
Visit 1	74	139.4	11.4	(137.2, 142.5)	95.2	7.5	(93.5, 96.9)
Visit 5	74	120.1	12.4	(117.3, 123.0)	81.2	6.8	(79.7, 82.8)

CI — confidence interval; SD — standard deviation

Table 6. Mean peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the first and the last visit of the trial

		Peripheral SBP [mmHg]			Peripheral DBP [mmHg]		
Visit	N	Average	SD	Asymptomatic CI	Average	SD	Asymptomatic CI
Visit 1	74	151.6	10.5	(149.2, 154.1)	94.2	7.6	(92.4, 95.9)
Visit 5	74	130.7	11.6	(128.0, 133.4)	80.4	6.7	(78.8, 81.9)

CI — confidence interval; SD — standard deviation

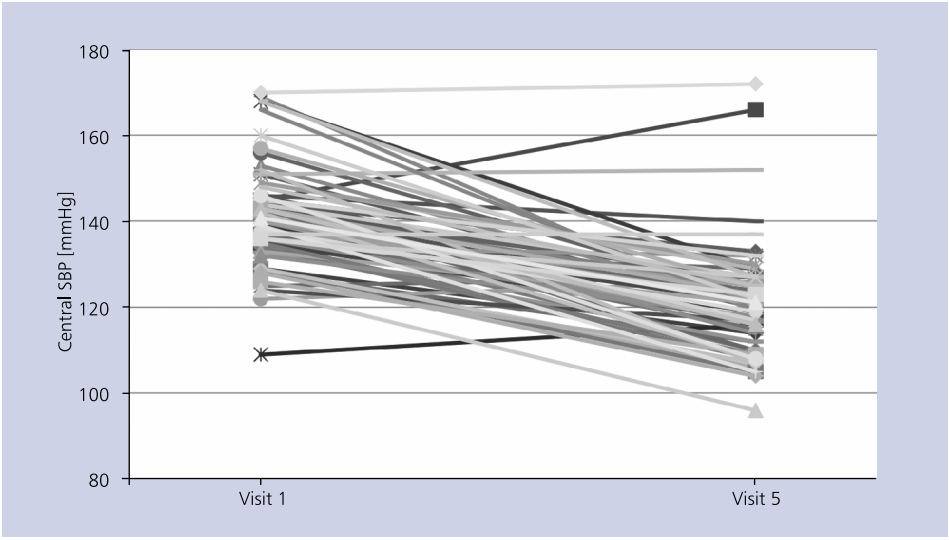

Figure 2. Central systolic blood pressure (SBP) on the first and the last visit for 74 patients from subgroup

from the first to the final visit of the trial. The absolute and relative decrease of PWV between monotherapy and combination therapy was statistically insignificant meaning that the improvement of aortic stiffness between these two groups was statistically insignificant.

Thirty nine patients, from whom the PWV data on the first and the last visit were obtained, were included in the PP analysis. Nine patients were included in the combination therapy group and 30 patients in the monotherapy group.

Table 7 shows the mean PWV values on the first and the last visit of the trial. The mean absolute decrease of PWV from the first to the last visit for combination therapy and monotherapy group were 1.87 ± 3.15 m/s (mean relative

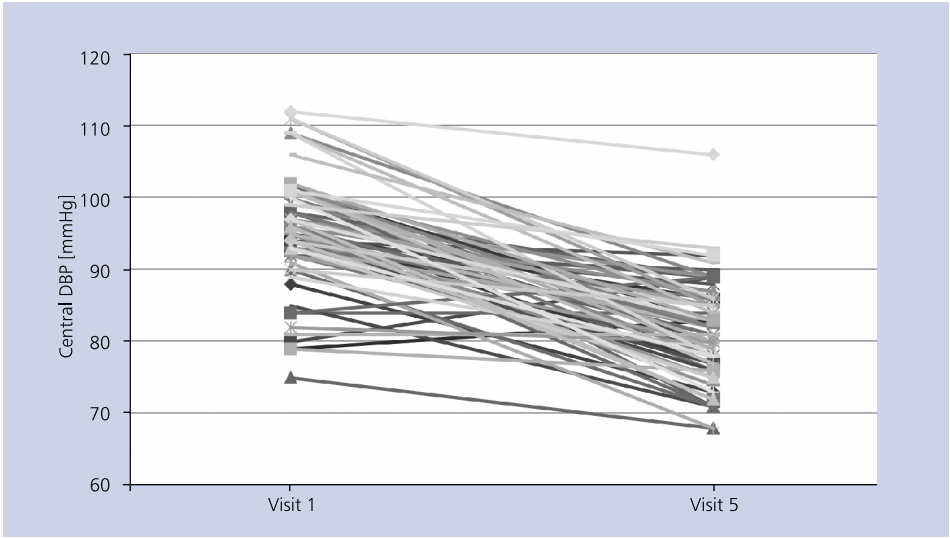

Figure 3. Central diastolic blood pressure (DBP) on the first and the last visit for 74 patients from subgroup

Table 7. The pulse wave velocity values during the trial for patients treated with monotherapy or combination therapy

	Combination therapy			Monotherapy		
Visit	N	Average	SD	N	Average	SD
Visit 1*	9	11.9	2.1	30	9.2	2.3
Visit 5	9	10.1	3.9	30	8.5	1.9

*Combination treatment was firstly introduced on visit 3 and additionally on visit 4; SD — standard deviation

Table 8. The augmentation index values during the trial for patients treated with monotherapy or combination therapy

	Combination therapy			Monotherapy		
Visit	N	Average	SD	N	Average	SD
Visit 1*	9	25.0	8.9	30	16.5	16.0
Visit 5	9	18.1	13.6	30	18.2	13.0

*Combination treatment was firstly introduced on visit 3 and additionally on visit 4; SD — standard deviation

decrease of PWV was 16.0 ± 27.8%) and 0.63 ± 0.86 m/s (mean relative decrease of PWV was 5.9 ± 8.6%), respectively.

The mean absolute and relative decrease of PWV between monotherapy and combination therapy group was statistically insignificant.

Effect of treatment on aortic AIx (PP analysis)

The data on AIx were obtained on the first and the last visit of the trial in a subgroup of patients. 39 patients, from whom the AIx data on the first and the last visit were obtained, were included in the PP analysis. Nine patients were included in the combination therapy group and 30 patients in the monotherapy group.

Table 8 shows the mean AIx values on the first and the last visit of the trial. The mean absolute decrease of AIx from the first to the last visit for combination therapy was 6.89 ± 13.41, while in the monotherapy group, the mean AIx increased from the first to the last visit for 1.73 ± 10.19.

The mean absolute difference of AIx between monotherapy and combination therapy group was statistically insignificant.

Absolute (mean) differences in CBP reduction versus peripheral BP reduction versus baseline values (PP analysis)

The data on central and peripheral BP were obtained on the first and the last visit of the trial in a subgroup of patients. 39 patients, from whom the PWV data on the first and the last visit were obtained, were included in the PP analysis. Nine patients were included in the combination therapy group and 30 patients in the monotherapy group.

Table 9. Mean central systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the first and the last visit of the trial for patients treated with monotherapy or combination therapy

	Combination therapy					Monotherapy				
	N	SBP [mmHg]		DBP [mmHg]		N	SBP [mmHg]		DBP [mmHg]	
Visit		Average	SD	Average	SD		Average	SD	Average	SD
Visit 1*	9	153.7	12.3	100.6	9.5	30	134.6	9.6	93.7	6.2
Visit 5	9	123.1	17.7	81.7	5.9	30	116.9	8.6	80.2	6.3

*Combination treatment was firstly introduced on visit 3 and additionally on visit 4; SD — standard deviation

Table 10. Mean peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the first and the last visit of the trial for patients treated with monotherapy or combination therapy

	Combination therapy					Monotherapy				
	N	SBP [mmHg]		DBP [mmHg]		N	SBP [mmHg]		DBP [mmHg]	
Visit		Average	SD	Average	SD		Average	SD	Average	SD
Visit 1*	9	164.56	10.5	99.56	9.5	30	147.6	8.36	92.6	6.5
Visit 5	9	137.33	17.5	80.44	5.3	30	129.27	8.74	79.2	6.5

*Combination treatment was firstly introduced on visit 3 and additionally on visit 4; SD — standard deviation

The Tables 9 and 10 represent the mean central and peripheral SBP and DBP in patients, treated with monotherapy or combination therapy, on the first and the last visit of the trial. The mean absolute decrease of central SBP and DBP were 30.56 ± 21.44 mmHg (mean relative decrease was 19.4 ± 13.7%) and 18.89 ± 10.94 mmHg (mean relative decrease was 18.0 ± 11.4%) for the combination therapy group and 17.73 ± 10.69 mmHg (mean relative decrease was 12.9 ± 7.8%) and 13.50 ± 9.31 mmHg (mean relative decrease was 14.0 ± 9.5%) for the monotherapy group, respectively.

On the other hand, the mean absolute decrease of peripheral SBP and DBP were 27.22 ± 19.32 mmHg (mean relative decrease was 16.3 ± 11.1%) and 19.11 ± 11.04 mmHg (mean relative decrease was 18.4 ± 11.6%) for the combination therapy group and 18.33 ± 10.50 mmHg (mean relative decrease was 12.2 ± 6.9%) and 13.40 ± 9.56 mmHg (mean relative decrease was 14.0 ± 9.8%) for the monotherapy group, respectively.

The decrease of both central and peripheral mean SBP and DBP between the combination therapy and monotherapy group were statistically insignificant.

DISCUSSION

In an international, multicentre, open-label, prospective phase IV trial the efficacy and safety of valsartan or its combination with HCTZ in patients with mild to moderate arterial hypertension was studied. In the VICTORY trial [9], 365 patients from five countries were included. Prior to the start of the active treatment, previously treated patients had to undergo one week of wash-out period. Patients who satisfied all inclusion criteria were included into the trial. All patients started the active treatment with valsartan in a dose of 80 mg (except in Russia, where previously treated patients started the treatment with valsartan in a dose of 160 mg — request from ethical committee — which did not have any influence on study results), which have been titrated on each control visit according to the dosing scheme and achievement of target BP.

In the subgroup of 74 patients, the mean absolute decrease of PWV from the first to the last visit was 0.95 ± 1.87 m/s and was statistically significant ($p < 0.0001$). According to the Moens-Korteweg equation, these results prove that valsartan and fixed combination of valsartan and HCTZ in patients with mild to moderate arterial hypertension reduce aortic stiffness. Treatment with valsartan may cause beneficial structural modifications in the arterial wall. Our novel findings that in patients with arterial hypertension ARB modulates arterial stiffness may, at least in part, explain the favourable cardiovascular protective effects observed with the renin–angiotensin system inhibition in several randomised controlled studies [11–14].

Increased aortic stiffness is likely to be attributable to an increase in intrinsic wall stiffness rather than raised BP alone. As higher elevated aortic pulse wave velocity (AoPWV) can adversely affect central pressure and cardiac function, simply lowering peripheral BP may be insufficient. Although no clinical trial to date has demonstrated that differential lowering of AoPWV with medical treatment results in different cardiac or renal outcomes, our work establishes a platform to address these important question in future clinical studies.

In the same subgroup of patients, central and peripheral BP as well as AIx were also measured. The mean absolute

and relative decreases of central and peripheral BP were both statistically significant ($p < 0.0001$). Results if AIx, on the other hand, did not show any statistically significant differences between the values on the first and the final visit.

CBP and AIx measurements do not necessarily reflect the same arterial wall properties as measured by PWV. CBP and AIx mirror changes in pressure wave reflection from distal sites (resistance vessels) where impedance mismatch occurs and are only indirect surrogate markers of aortic stiffness. Although increased aortic stiffness is responsible for the velocity of the pressure wave transmission, the intensity of the wave reflection, and thereby CBP and AIx, is determined primarily by the reflective properties of the vasculature which can be modulated independently of arterial stiffening [15].

The difference in BP decrease between the monotherapy and combination therapy groups from visit 3 to visit 5 was statistically significant ($p < 0.0001$), taking in mind that combination therapy was initiated in patient, who did not reach target BP on visit 3 and visit 4.

There are limitations to our study. The open design of the study did not allow us to compare the effect to another treatment. We did not make direct measurements of the mechanical properties of the vessel wall. This would require an invasive technique not applicable in a clinical study and AoPWV, measured by applanation tonometry, which is a well-established, accurate, and sensitive marker of central arterial stiffness.

The mean relative and absolute decrease of all other secondary efficacy endpoint parameters, which relates to the subgroup of patients, were statistically insignificant between the combination therapy and monotherapy. Data on PWV and CBP were collected on the first and the last visit of the trial. Thus, the comparison of data between monotherapy with combination therapy is in this case not relevant and does not give exact information whether the combination therapy provides better results than monotherapy or not due to the fact, that combination treatment was not used in a subgroup of patients throughout the whole trial. Statistical significance of differences between combination therapy and monotherapy was also proven for mean values of SBP and DBP, mean peripheral and central SBP and mean PWV on specific control visits.

CONCLUSIONS

The results of the present VICTORY trial shows that valsartan and fixed combination of valsartan and HCTZ effectively reduce the BP in patients with mild to moderate arterial hypertension. Furthermore, based on results of PWV, both medicines improve and reduce aortic stiffness, thus these results could have clinical implications and should emphasize the need for early therapies which, beyond brachial BP lowering, provide a beneficial reduction in PWV. Reduction of central SBP and DBP was greater than brachial SBP and DBP.

Acknowledgements: *VICTORY trialist group: from Slovenia: Salobir Barbara, Erhatič Andrej, Pintar Romana, Rus Primož, Bavdek Dušan, Štefančič Gašperšič Marija, Benedičič Nikolaj, Žorž Gojmir; from Croatia: Krstačić Goran, Božič Borka, Prkačin Ingrid, Kranjčević Stjepan, Počanić Darko; from Czech Republic: Filipovsky Jan, Souček Miroslav; from Russian Federation: Arkhipov Mikhail, Grinstein Yuriy, Ostroumova Olga, Galyavich Albert, Nedogoda Sergey, Rotar Oxana, Khaisheva Larisa; from Ukraine: Swischenko Eugenia, Dolzhenko Marina, Kushnir Svitlana, Radchenko Ganna.*

Source of funding: *This study was sponsored by KRKA, d. d., Novo mesto, Slovenia.*

Conflict of interest: *Rok Accetto and Jiri Widimsky Jr. have received honoraria from Krka, d. d., Novo mesto, Ljubljana, Slovenia, Breda Barbic Zagar is Medical Director at Krka, d. d., Novo mesto, Ljubljana, Slovenia. For the remaining authors no conflicts of interest were declared.*

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Cite this article as: Accetto R, Widimsky Jr. J, Vincelj J, et al. The efficacy and safety of valsartan and a combination of valsartan and hydrochlorothiazide in the treatment of patients with mild to moderate arterial hypertension: a subgroup analysis of the effect of valsartan and its combination with hydrochlorothiazide on pulse wave velocity and central blood pressure. Kardiol Pol. 2018; 76(2): 328–337, doi: 10.5603/KP.a2017.0240.