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The Efficacy and Tolerability of a Fixed Combination of Perindopril and Indapamide in the Treatment of Unregulated Essential Hypertension – a Post-marketing Study

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Abstract

Objective. The objective of this non-interventional post-marketing clinical trial was to analyze the antihypertensive effect and safety of a fixed combination of perindopril and indapamide in the treatment of unregulated essential hypertension. **Patients and Methods.** The prospective clinical trial included patients aged 20 to 75 years with essential hypertension and blood pressure values ≥140/90 mmHg at baseline. On the basis of the investigator's decision, patients received 2 mg perindopril + 0.625 mg indapamide (group 2+0.625) or 4 mg perindopril + 1.25 mg indapamide (group 4+1.25). **Results.** The study included 1173 patients (426 patients in group 2+0.625 and 747 patients in group 4+1.25) at 27 investigational centers in Bosnia and Herzegovina. Mean blood pressure values at baseline and visits after nine months were significantly higher in the 4+1.25 group compared to the 2+0.625 group. There was a significant drop in systolic and diastolic blood pressure in both groups. The target values of systolic and diastolic blood pressure, according to the European Society of Cardiology (2018), were reached after nine months of therapy by more than 80% of patients in the 2+0.625 group, and this number was significantly higher compared to the 4+1.25 group where more than 60% of patients reached target values. Newly diagnosed patients had a better response to therapy. The percentage of patients receiving additional antihypertensive therapy decreased by the end of the study. Age, gender and the existence of diabetes mellitus were identified as negative predictors of target blood pressure achievement. The therapy showed a good safety profile. **Conclusion.** A fixed combination of perindopril and indapamide was effective and safe in the treatment of unregulated essential hypertension.

Key Words: Perindopril and Indapamide ▪ Fixed Combination ▪ Uncontrolled Hypertension.

Introduction

Hypertension affects about 900 million adults worldwide and is the leading global cause of death and disability (1). The Task Force for the Management of Arterial Hypertension of the ESC and the ESH recommend that when blood pressure-lowering drugs are used, the first objective should be to lower blood pressure to <140/90 mmHg in all patients (2). Provided that the treatment is well tolerated, treated blood pressure values should be targeted to 130/80 mmHg or lower in most patients, although in some groups the evidence is less compelling. In older patients (>65 years), systolic blood pressure should be targeted to between 130 and 140 mmHg, and diastolic blood pressure to <80 mmHg. Treated systolic blood pressure should not be targeted to <120 mmHg (3).

The guidelines from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) from 2018 recommend initiating antihypertensive treatment with a two-drug combination of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), plus calcium channel blockers (CCB) or a diuretic, providing more rapid control of blood pressure than monotherapy (2). Use of an ACE inhibitor combined with a diuretic is a well-established antihypertensive combination that is very effective because of their different, yet synergistic, mechanisms of action (3). Contrary to commonly used thiazide diuretics that have negative metabolic effects, in terms of increasing the risk for diabetes and hyperlipidemia, indapamide has neutral metabolic effects (4-6). The antihypertensive effect of indapamide is due to its dual mechanism of action: both natriuretic diuretic and vasodilatory effects. It is highly lipophilic with a tendency to accumulate in the plasmatic membrane of smooth muscle cells, reducing transmembrane calcium flux, with a vasodilatory effect (7).

Although a fixed combination of perindopril and indapamide is standard care (2), there are no studies evaluating the efficacy and safety of this combination in Bosnia and Herzegovina. Also, it is of interest to evaluate independent predictors of target blood pressure achievement, and monitor concomitant medications and comorbidities in patients treated with this combination.

Therefore, the objectives of this study were: (i) to analyze the antihypertensive effect and safety of a fixed combination of perindopril and indapamide in the treatment of unregulated essential hypertension, (ii) to determine independent predictors of target blood pressure achievement, and (iii) to analyze concomitant medications and comorbidities in patients from Bosnia and Herzegovina.

Materials and Methods

Study Design

This prospective, non-interventional, post-marketing clinical trial was conducted in 27 investigational centers in Bosnia and Herzegovina. Patients aged 20 to 75 years with essential hypertension and blood pressure values ≥140/90 mmHg at baseline were included. On the basis of the investigator's decision, patients received either 2 mg perindopril+0.625 mg indapamide (Hypressin Plus® 2 mg/0.625 mg tablets, Bosnalijek d.d., Bosnia and Herzegovina) and were assigned to the 2+0.625 group, or 4 mg perindopril+1.25 mg indapamide (Hypressin Plus® 4 mg/1.25 mg tablets, Bosnalijek d.d., Bosnia and Herzegovina) and were assigned to the 4+1.25 group.

The exclusion criteria were: a positive history of angioneurotic edema, unregulated hypertension after administration of more than three antihypertensives, a mental/emotional disorder, malignant disease, severe liver and kidney damage, dialysis requirements, untreated decompensated heart failure, hypokalemia, pregnancy, breastfeeding, hypersensitivity to drug components, and concomitant use of drugs containing aliskiren, immunosuppressive, allopurinol or procainamide therapy.

The primary objective was defined as a reduction of blood pressure to normal values according to the ESC and the ESH guidelines (8, 9). The secondary objective was evaluation of the safety and tolerability of perindopril + indapamide (Hypressin Plus®) tablets in the treatment of unregulated essential hypertension.

Ethics Statement

The clinical trial was approved by the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina. The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. Before any procedure started, each patient signed an informed consent form.

Evaluation of Efficacy and Tolerability

The efficacy of perindopril + indapamide fixed combination in the treatment of non-regulated essential hypertension was evaluated by measurement of heart rate, and systolic and diastolic blood pressure. Tolerability was evaluated by monitoring the incidence of adverse drug events with an assessment of

the association between the use of the drugs and the occurrence of adverse reactions by the physician. Blood concentrations of potassium, sodium, creatinine, urea, and glucose were also monitored.

Data Collection

Data collection for each patient was performed over a nine month period (baseline, first follow up visit three months after baseline, second follow up visit six months after baseline, and third follow up visit nine months after baseline). At the baseline, demographic data about the patient were collected, together with their heart rate, systolic and diastolic blood pressure, and the results of laboratory tests (blood concentrations of potassium, sodium, creatinine, urea, and glucose). Previous concomitant therapy and newly included therapy were recorded. At the first and second control visits, heart rate, systolic and diastolic blood pressure, together with adverse events and therapy to be used or continued, were recorded. At the third and last follow up visit, the investigator recorded the heart rate, systolic and diastolic blood pressure, and the results of laboratory tests (blood concentrations of potassium, sodium, creatinine, urea, and glucose). Adverse events were monitored at all timepoints.

Statistical Analysis

The Kolmogorov-Smirnov test was used to determine normal distribution of numerical data. The results were presented as mean ($\bar{x}$) and standard deviation (SD) for data that followed normal distribution, or as median and interquartile range (IQR) for data that did not follow normal distribution. The average values of systolic and diastolic blood pressure estimated at different time intervals were shown with a 95% confidence interval. The differences in the mean values of heart rate, blood pressure, and laboratory parameters between the two treatment groups were tested by the Student t-test for independent samples if the variables followed normal distribution, and the Mann–Whitney U test for variables that did not follow normal distribution. To test the differences in blood pressure changes estimated at different time intervals (at baseline, and after 3, 6 and 9 months), the ANOVA (analysis of variance) test was used for repeated measurements, after which an appropriate *post hoc* test was applied. The differences in the proportion of patients who achieved target values of systolic and diastolic blood pressure between the groups were tested by the Chi square test. The logistic regression analysis was used to examine the independent predictors of predefined outcomes. Gender, age, newly discovered/pre-existing hypertension, duration of hypertension, diabetes mellitus, smoking, and concomitant antihypertensive therapy were covariates included in the logistics analysis. Outcome predictors were presented as odds ratio and a 95% confidence interval. Statistical significance was taken to be at the level of $P < 0.05$.

Results

The study was conducted in the period between June 2019 and November 2020. Out of 1373 patients screened, 1173 patients were enrolled (426 patients in the 2+0.625 group and 747 patients in the 4+1.25 group). Patients were monitored for the following nine months at three visits (after three, six and nine months) where blood pressure was assessed at each visit, and some patients changed treatment group, as decided by the investigator. A diagram of the flow of patient distribution into the therapeutic groups is presented in Figure 1.

At the baseline visit, patients in the 4+1.25 group compared to the 2+0.625 group were significantly older, had a higher body mass index (BMI), higher waist circumference, more diabetes mellitus, more pre-existing hypertension that had lasted longer, and higher mean values of systolic and diastolic blood pressure and blood glucose levels. No differences in potassium, sodium, creatinine and urea levels were observed between the two study groups (Table 1).

The antihypertensive concomitant therapy used during the study is shown in Table 2. The most common additional antihypertensive drug was a beta blocker in both treatment groups. The use of additional antihypertensive drugs decreased from baseline to the visit after six months (Table 2).

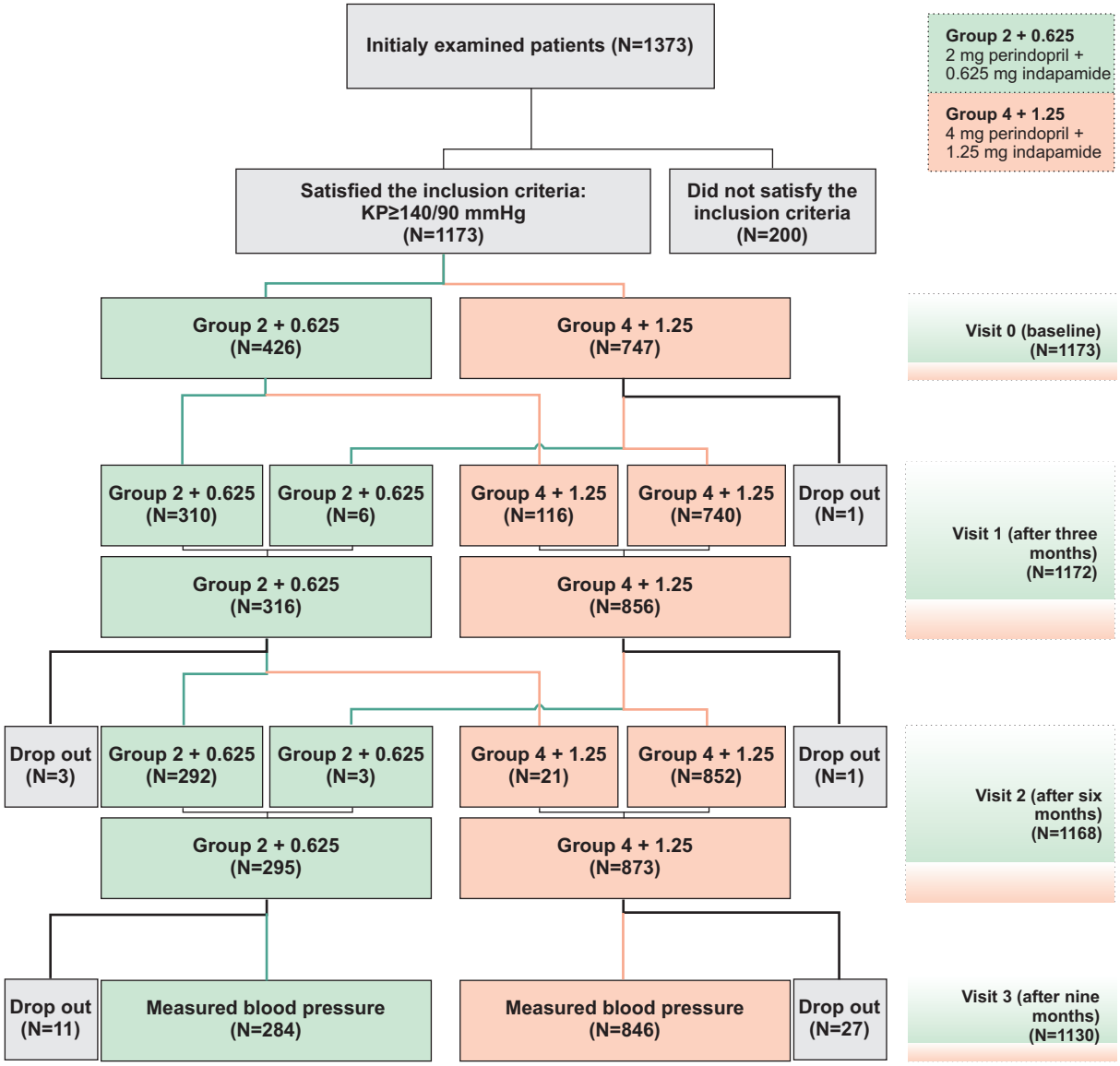

Figure 1. The flow of patient distribution into therapeutic groups

Table 1. Demographic and Clinical Characteristics of Patients with Unregulated Hypertension at the Baseline Visit in Relation to the Prescribed Therapy

Characteristics	Group 2+0.625 (N=426)	Group 4+1.25 (N=747)	P-value
Age (years)	53.6±11.6	59.8± 11.3	<0.001‡
Gender (Male/Female)	198 (46.9%)/224 (53.1%)	386 (51.9%)/358 (48.1%)	0.110‖
Height (cm)	173.2±12.6	174.6± 9.7	0.036‡
Weight (kg)	81.5±11.3	84.6±13.6	<0.001‡
Body mass index	27.1±3.4	27.9±3.8	0.001‡
Waist circumference (cm)	94.1±11.1	99.1±12.5	<0.001‡
Pre-existing HTN*	196 (46.0%)	528 (70.7%)	<0.001‖
Newly diagnosed HTN*	225 (52.8%)	216 (28.9%)	
HTN* duration (years)	5.0 (3.0-10.0)	8.0 (4.0-12.5)	0.001§
Smoker	201 (47.2%)	303 (40.6%)	0.030‖
Former smoker	32 (7.5%)	65 (8.7%)	
Number of cigarettes	21.6±8.8	22.0±8.3	0.650‡
Consumes alcohol	86 (20.2%)	155 (20.7%)	0.820‖
Sedentary lifestyle	186 (43.7%)	370 (49.5%)	0.070‖
DM†	51 (12.0%)	164 (22.0%)	<0.001‖
Type 2	40 (78.4%)	135 (82.3%)	-
Type 1	0	4 (2.4%)	-
Duration of DM† (years)	7.0 (3.0-10.0)	7.0 (5.0-10.0)	0.160§
Systolic blood pressure	156.2±10.6	161.7±14.3	<0.001‡
Diastolic blood pressure	94.7±5.5	97.3±6.9	<0.001‡
Heart rate	82.3±12.8	82.0±12.7	0.700‡
Potassium (mmol/L)	4.4±0.5	4.4±0.5	0.300‡
Sodium (mmol/L)	139.4±8.2	139.5±10.9	0.920‡
Creatinine (mmol/L)	91.6±18.5	93.0±18.4	0.230‡
Urea (mmol/L)	6.8±4.7	6.9±4.0	0.730‡
Glucose (mmol/L)	5.8±2.0	6.3±3.4	0.014‡

*Hypertension; †Diabetes mellitus; ‡Student t-test; §Mann–Whitney U test; ‖Chi-square test.

Table 2. Concomitant Antihypertensive Therapy at the Baseline Visit and after Three and Six Months of Follow-up in Relation to Therapeutic Groups

Visit	Antihypertensive therapy	Group 2+0.625 N (%)	Group 4+1.25 N (%)
Baseline visit	Calcium channel blockers	3 (0.7)	38 (5.1)
	Beta-blockers	23 (5.4)	57 (7.6)
	Diuretic	1 (0.2)	10 (1.3)
	ACE inhibitors	-	12 (1.6)
Visit after three months	Calcium channel blockers	2 (0.6)	52 (6.1)
	Beta-blockers	10 (3.2)	55 (6.4)
	Diuretic	-	9 (1.1)
	ACE inhibitors	-	25 (2.9)
Visit after six months	Calcium channel blockers	1 (0.3)	38 (4.4)
	Beta-blockers	2 (0.7)	34 (3.9)
	Diuretic	-	10 (1.1)
	ACE inhibitors	-	13 (1.5)

Systolic and Diastolic Blood Pressure During Therapy

In the 2+0.625 group, mean systolic blood pressure values dropped significantly from baseline to the visit after nine months, with a mean reduction of -27.9 mmHg; 95% CI (-29.4 to 26.5); P<0.001 (Table 3). Also, mean diastolic blood pressure values decreased significantly between baseline and the visit after nine months, with a mean reduction of -15.3 mmHg; 95% CI (-16.2 to -14.5); P=0.014 (Table 3).

In the 4+1.25 group, mean systolic blood pressure values dropped significantly from baseline to the visit after nine months, with a mean reduction of -29.9 mmHg; 95% CI (-30.8 to -28.9); P<0.001 (Table 3). Also, mean diastolic blood pressure values dropped significantly from baseline to the visit after nine months, with a mean reduction of -16.4 mmHg; 95% CI (-16.9 to -15.9); P<0.001 (Table 3).

Mean systolic and diastolic blood pressure values were significantly higher in the 4+1.25 group versus the 2+0.625 group at baseline and the visit after nine months (Table 3).

The mean reduction in systolic and diastolic blood pressure was significantly higher in the 4+1.25 group compared to the 2+0.625 group at all time points of patient follow-up (Table 4). The percentages of patients reaching the target values of systolic and diastolic blood pressure, defined according to ESC (2018) (8, 9), are presented in Table 5.

Table 3. Mean Values of Systolic and Diastolic Blood Pressure*

Blood pressure (mmHg)		Group 2+0.625 (Mean±SD)	Group 4+1.25 (Mean±SD)	P-value*
Systolic	Baseline visit	156.2±10.6	161.7±14.3	<0.001
	Visit after three months	141.4±10.6	143.0±13.8	0.380
	Visit after six months	132.8±10.8	135.7±10.5	0.650
	Visit after nine months	128.8±7.5	131.8±9.2	0.005
Diastolic	Baseline visit	94.7±5.5	97.3±6.9	<0.001
	Visit after three months	86.5±6.2	86.9±6.7	0.070
	Visit after six months	82.3±5.5	83.3±7.2	0.670
	Visit after nine months	79.6±4.3	81.1±5.5	0.020

*Student t-test.

Table 4. Average Reduction of Systolic and Diastolic Blood Pressure at Baseline and Three Follow up Visits*

Blood pressure (mmHg)		Group 2+0.625 Median with IQR*	Group 4+1.25 Median with IQR*	P-value†
Systolic	Three months vs. baseline	-14.8 (-15.7 to -13.9)	-18.5 (-19.3 to -17.7)	<0.001
	Six months vs. baseline	-23.7 (-25.2 to -22.2)	-26.0 (-26.9 to -25.1)	0.008
	Nine months vs. baseline	-27.9 (-29.4 to -26.5)	-29.9 (-30.8 to -28.9)	0.030
Diastolic	Three months vs. baseline	-8.2 (-8.7 to -7.6)	-10.4 (-10.9 to -9.9)	<0.001
	Six months vs. baseline	-12.3 (-13.4 to -11.0)	-14.0 (-14.4 to -13.4)	0.002
	Nine months vs. baseline	-15.3 (-16.2 to -14.5)	-16.4 (-16.9 to -15.9)	0.038

*Interquartile range. †Analysis of Variance (ANOVA) test followed by Tukey or Games-Howell post-hoc test.

Table 5. Proportion of Patients with Achieved Target Values of Systolic and Diastolic Blood Pressure according to European Society of Cardiology ECS (2018) in Relation to the Treatment Group

Achieved target blood pressure		Group 2+0.625	Group 4+1.25	χ^2 and P-value
Systolic	Visit after three months	107/426 (25.1%)	157/747 (21.0%)	χ^2=2.60; P=0.011
	Visit after six months	192/316 (60.8%)	391/856 (45.7%)	χ^2=21.00; P<0.001
	Visit after nine months	241/295 (81.7%)	538/873 (61.7%)	χ^2=39.60; P<0.001
Diastolic	Visit after three months	134/426 (31.5%)	220/747 (29.5%)	χ^2=0.52; P=0.510
	Visit after six months	199/316 (63.0%)	452/856 (52.8%)	χ^2=9.70; P=0.002
	Visit after nine months	246/295 (83.4%)	596/873 (68.3%)	χ^2=25.10; P<0.001

Independent Predictors of Achieving Systolic and Diastolic Blood Pressure Targets according to the ESC (2018)

In the logistic regression analysis model, we examined the predictors for achieving the target values of systolic and diastolic blood pressure according to the ESC (2018), after three, six and nine months of therapy.

In the 2+0.625 group, age was a negative predictor of reaching target systolic and diastolic blood pressure after six months of therapy. Male gender was a negative predictor of reaching target systolic blood pressure after nine months of therapy, and target diastolic blood pressure after three months of therapy. The presence of diabetes mellitus was a negative predictor of reaching target diastolic blood pressure after three months of therapy (Table 6).

In the 4+1.25 group, age was a negative predictor of reaching target systolic blood pressure at all time points evaluated. Male gender was a negative predictor of reaching target diastolic blood pressure after three and nine months of therapy. The presence of diabetes mellitus was a negative predictor of reaching target systolic blood pressure after three months of therapy, and reaching target diastolic blood pressure after nine months of therapy. The number of additional antihypertensive drugs was a positive predictor of reaching target systolic blood pressure after three months of therapy (Table 6).

Table 6. Independent Predictors of Reaching Target Systolic and Diastolic Blood Pressure Obtained by the Logistic Regression Analysis

Therapy duration	Predictor	B coefficient*	P-value	Odds ratio†
Independent predictors of reaching target systolic blood pressure				
Group 2+0.625				
Three months	None identified	-	-	-
Six months	Age	-0.030	0.013	0.97 (0.95–0.99)
Nine months	Male gender	-0.700	0.040	0.50 (0.27–0.98)
Group 4+1.25				
Three months	Age	-0.030	0.005	0.97 (0.96–0.99)
Three months	Diabetes mellitus	-0.600	0.027	0.57 (0.34–0.94)
Three months	Number‡	0.400	0.034	1.50 (1.03–2.10)
Six months	Age	-0.020	0.001	0.98 (0.96–0.99)
Nine months	Age	-0.020	0.003	0.98 (0.97–0.99)
Independent predictors of reaching target diastolic blood pressure				
Group 2+0.625				
Three months	Male gender	-0.600	0.009	0.55 (0.35–0.86)
Three months	Diabetes mellitus	-0.960	0.040	0.38 (0.15–0.96)
Six months	Age	-0.050	<0.001	0.95 (0.93–0.98)
Nine months	None identified	-	-	-
Group 4+1.25				
Three months	Male gender	-0.380	0.030	0.69 (0.50–0.96)
Six months	None identified	-	-	-
Nine months	Male gender	-0.020	0.008	0.98 (0.97–0.99)
Nine months	Diabetes mellitus	-0.500	0.008	0.61 (0.43–0.88)

*B coefficient showing the change in log odds that occur for a one-unit change in an independent variable when all other independent variables are kept constant; †95% confidence interval; ‡Number of added antihypertensive drugs.

Target values of systolic and diastolic blood pressure achieved in relation to the duration of hypertension

Compared to patients with pre-existing hypertension, a significantly higher number of patients with newly diagnosed hypertension reached the target values of systolic blood pressure after six months in both groups (Table 7). Compared to patients with pre-existing hypertension, a significantly higher number of patients with newly diagnosed hypertension in the 4+1.25 group reached the target values of diastolic blood pressure after three and six months. However, in the 2+0.625 group there was no significant difference in the proportion of patients who reached the target values in relation to the presence of hypertension (Table 7).

Heart Rate

Heart rate dropped significantly during the nine-month therapy in both study groups, although the mean values were within the reference range. The mean heart rate in the 2+0.625 group was significantly lower at the second and third follow up visits compared to the 4+1.25 group (Table 8).

Results of Laboratory Tests after Nine Months of Therapy

The mean values of potassium, sodium, creatinine, urea and glucose remained within the reference intervals, and there was no significant difference between the examined groups. Mean glucose values remained significantly higher in the 4+1.25 group (Table 9). Hypokalemia occurred in 1.0% patients in the 2+0.625 group and 0.5% patients in the 4+1.25 group (Table 9).

Table 7. Proportion of Patients with Pre-existing and Newly Diagnosed Hypertension Who Reached the Target Values of Systolic and Diastolic Blood Pressure in the Period of Three, Six and Nine Months of Follow-up in Relation to the Therapeutic Group

Therapy duration	Group 2+0.625			Group 4+1.25		
	Hypertension (mmHg)			Hypertension (mmHg)		
	Pre-existing	Newly diagnosed	P-value*	Pre-existing	Newly diagnosed	P-value*
Reaching target systolic blood pressure						
Three months	46/196 (23.5%)	60/225 (26.7%)	0.500	104/528 (19.7%)	53/216 (24.5%)	0.170
Six months	75/137 (54.7%)	116/174 (66.7%)	0.035	253/586 (43.2%)	138/267 (51.7%)	0.022
Nine months	100/122 (82.0%)	138/168 (82.1%)	1.000	361/600 (60.2%)	178/270 (65.9%)	0.110
Reaching target diastolic blood pressure						
Three months	54/196 (27.6%)	79/225 (35.1%)	0.110	140/528 (26.5%)	79/216 (36.6%)	0.008
Six months	87/137 (63.5%)	110/174 (63.2%)	1.000	295/586 (50.3%)	157/267 (58.8%)	0.020
Nine months	105/122 (86.1%)	136/168 (81.0%)	0.270	411/600 (68.5%)	185/270 (68.5%)	1.000

*Chi-square test.

Table 8. Heart Rate in Patients in Relation to the Treatment Group during the Nine-month Follow-up. Data Are Presented as Mean±SD*

Heart rate	Group 2+0.625	Group 4+1.25	P-value*
Baseline visit	82.3±12.8	82.0±12.7	0.700
After three months	77.2±9.7	77.3±9.6	0.820
After six months	74.3±8.0	75.4±8.6	0.040
After nine months	72.6±7.3	73.8±8.1	0.010
P-value† (baseline visit vs. nine months)	<0.001	<0.001	

*Student t-test. †Analysis of Variance (ANOVA) test followed by Tukey or Games-Howell post-hoc test.

Table 9. Laboratory Parameters After Nine Months of Follow-up in Relation to Therapeutic Groups. Values are Presented as Mean±SD or Absolute Numbers and Percentages

Parameters (mmol/l)	Group 2+0.625	Group 4+1.25	P-value*
Potassium	4.4±0.4	4.6±0.5	0.500
Sodium	139.9±5.0	139.7±6.2	0.920
Creatinin	91.4±54.9	93.9±57.8	0.550
Urea	6.4±3.9	7.0±5.9	0.130
Glucose	5.5±1.3	5.9±1.4	<0.001
Hypokalemia†	3/295 (1.0%)	4/873 (0.5%)	-

*Student t-test; †<3.5 mmol/l.

Adverse Events

The most common side effects at the first follow up visit were nausea in the 2+0.625 group (1.2%) and cough in the 4+1.25 group (0.4%) (Table 10). The prevalence of side effects during the subsequent visits decreased, and after nine months of therapy, a cough was present in only one patient in the 2+0.625 group and in 2 patients in the 4+1.25 group (Table 10).

Discussion

In this prospective, non-interventional, post marketing study, a fixed combination of perindopril and indapamide was shown to be effective and safe in the treatment of unregulated essential hypertension. Mean blood pressure decreased significantly, and most of the patients reached the blood pressure target after nine months of therapy with a better response to therapy in newly diagnosed patients. Usage of additional antihypertensive therapy decreased over time. Changes in blood pressure were accompanied by decreases in heart rate. Negative predictors of target blood pressure achievement were age, gender and co-existence of diabetes mellitus.

Diabetes and hypertension are considered as "bad companions." Large hypertension outcome trials comparing antihypertensive drugs with a placebo or usual care in patients with diabetes and hypertension have only compared thiazide type

Table 10. Adverse Events in Patients after Three, Six and Nine Months of Therapy in Relation to Treatment Groups

Therapy duration (months)	Adverse event	Group +0.625 (N; %)	Group 4+1.25 (N; %)
Three	Cough	4 (0.9)	3 (0.4)
	Nausea	5 (1.2)	2 (0.3)
	Headache	-	1 (0.1)
	Diarrhea	-	2 (0.3)
	Dizziness	-	1 (0.1)
	Tinnitus	-	2 (0.3)
	BP* oscillation	-	1 (0.1)
Six	Cough	3 (0.9)	1 (0.1)
	Tachycardia	1 (0.3)	-
	Hypotension	-	2 (0.2)
	Constipation	-	1 (0.1)
	Dizziness	-	1 (0.1)
	Tinnitus	-	1 (0.1)
Nine	Cough	1 (0.3)	2 (0.2)
	Hypotension	-	1 (0.1)

*Blood pressure.

diuretics and calcium-channel blockers. These drugs have been shown to reduce cardiovascular disease events and mortality. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study, fixed combination perindopril and indapamide, as the thiazide type diuretic, significantly reduced all-cause mortality by 14%, cardiovascular disease mortality by 18% and combined macrovascular and microvascular events by 9% and reduced separate macrovascular outcomes by 8% and microvascular outcomes by 9%, although not significantly (10). In patients with diabetes, a combination of a RAS-blocker and a thiazide-type diuretic might be the most reasonable initial antihypertensive regimen (10).

As shown in clinical studies, gender, as another negative predictor of target blood pressure has an influence on the dose-ranging of perindopril+indapamide combination in hypertension with its effects on systolic and pulse pressure. In hypertensive subjects, the low dose combination perindopril+indapamide (2+0,625) mg and (4+1,25) mg was the most effective in reducing blood pressure and avoiding hypokalemia compared to other combinations of perindopril and indapamide doses, and this result was more pronounced in women (11).

When considering age, resistant hypertension is more prevalent in elderly patients. In the Hypertension in the Very Elderly Trial (HYVET), patients in the "late elderly" group (≥ 80 years of age with elevated SBP) were randomized to receive indapamide, with the addition of perindopril if needed, or a placebo. In this study, the patients in the indapamide group had a 30% risk reduction for fatal and non-fatal stroke (12).

The results of our study are consistent with previous studies, and the therapy is in accordance with the European guidelines (ESC/ESH 2018) for the treatment of moderate to severe hypertension, that highly recommend initiation of treatment with a single pill combination containing two drugs (13). These single pill combinations have been found to be effective and to control blood pressure faster, especially when monotherapy is inadequate to achieve the target range of blood pressure (10, 11). The efficacy and safety of perindopril (an ACE inhibitor)+indapamide (a chlorosulphamoyl diuretic) has been proven through many studies. In daily medical practice, a combination of ACE inhibitors and a diuretic is the drug of choice for initial therapy or maintenance therapy. The combination of perindopril and indapamide has synergistic activity, resulting in lower required doses compared to monotherapies (10-12). Analysis of data from nearly 30,000 patients showed that 2/3 of patients (mostly on monotherapy: ACE-inhibitors, calcium channel antagonists and diuretics) do not have controlled blood pressure. In the PRETEND study (N=3,198 patients) 2/3 patients received concomitant therapy (lipid-lowering therapy, antithrombotic and antidiabetic therapy) and perindopril+indapamide was included as the first drug of choice in the treatment of blood pressure, or used as a replacement drug for prior antihypertensive therapy. Therapy with a fixed combination of perindopril+indapamide reduced blood pressure with a significantly improved control rate from 1.1 to 38.7%. The systolic blood pressure control rate improved from 3.1% to 44.15% and diastolic blood pressure control rate improved from 20.5% to 77.5%. The study confirmed the beneficial action of 2 mg perindopril+0.625 mg indapamide in daily clinical practice, where this combination effectively reduced blood pressure rates and pulse pressure in various patients (14). This fixed combination is more effective than monotherapy with 10 mg enalapril in the treatment of hypertension and subclinical organ damage, as well as cardiovascular events. The PICXL study showed that perindopril+indapamide, besides reducing hypertension, has positive effects on hypertrophy of the left ventricular and large blood vessels. Further, perindopril + indapamide reduces systolic and diastolic blood pressure, and reduces the albumin excretion rate (AER) in patients with type 2 diabetes (T2DM) (11, 15).

A multicenter, prospective, observational study showed that the fixed combination of 4 mg perindopril + 1.25 mg indapamide was effective in more than 90% of uncontrolled or newly diagnosed

patients with moderate to severe arterial hypertension, including patients with diabetes. During 90 days of therapy, systolic and diastolic blood pressures were significantly reduced and blood pressure was less than 140/90 mmHg (13).

In a study including 11,140 patients with T2DM (≥55 years), with isolated systolic hypertension, perindopril + indapamide combinations (2 mg+0.625 mg and 4 mg+1.25 mg) per day reduced mortality and major macrovascular and microvascular events, renal complications, and overall coronary diseases (16). In patients with T2DM, it is especially important to reduce cardiovascular and kidney diseases. Extensive data from clinical trials show that perindopril+indapamide therapy reduces mortality and vascular events in patients with T2DM (13, 17, 18). In obese patients, or those with metabolic syndrome, current recommendations for the treatment of hypertension (ESC/ESH, ACC/AHA, ISH) are not specified, but a single pill combination containing two drugs is preferred (3).

In our study, the treatment was well tolerated. The most common adverse reactions were cough and nausea, and all reactions were reduced by the end of the study (ninth month of therapy). Levels of sodium, potassium, creatinine, and urea were within the reference intervals, and there was no significant difference between the examined groups. The perindopril+indapamide single pill combination shows a higher antihypertensive effect with a smaller number of side effects compared to antihypertensive monotherapy. Co-administration of the two agents reduces the incidence of hypokalemia seen with indapamide alone (13, 14, 19). Other studies have also shown that adverse events with the fixed combination perindopril+indapamide (from 2 mg+0.625 mg to 8 mg+2.5 mg) are mild, and that this combination has a favorable safety profile in patients with mild, or moderate to severe hypertension (13, 20). Adverse events, such as a dry cough, headache, high fever, gastroesophageal reflux diseases, giddiness and paronychia, are often not associated with the therapy (13). Perindopril+indapamide therapy does not significantly change lipid parameters and serum electrolytes. Furthermore, there were no significant differences in the changes in carbohydrate metabolism parameters. Many studies have demonstrated the metabolic neutrality of this combination, and showed that it does not induce changes in potassium, creatinine, lipid and glucose profiles (11, 14, 17).

To our knowledge this is the first study to evaluate the use of another antihypertensive drug during perindopril+indapamide therapy. It was found that beta blockers are the most common antihypertensive therapy used along with the investigated fixed dose combination. The use of this concomitant therapy decreased during the study. The results suggest that patients receiving perindopril + indapamide reached the blood pressure target and the need for additional antihypertensive drugs decreased.

Limitations of the Study

The study was not placebo or comparator controlled, and the duration of the follow-up was nine months.

Conclusion

The fixed combination of perindopril and indapamide was effective and safe in the treatment of unregulated essential hypertension. There was a significant drop in systolic and diastolic blood pressure in both groups, while adverse events were mild and their number decreased over time. Newly diagnosed patients had a better therapy response. Age, gender and the existence of diabetes mellitus were identified as negative predictors of target blood pressure achievement.

What Is Already Known on This Topic:
The perindopril and indapamide single pill combination is effective therapy for essential hypertension, and known for fast achievement of target blood pressure values. It is recommended especially when monotherapy is inadequate for achieving the target range of blood pressure.

What This Study Adds:
This is the first prospective study conducted on the fixed combination of perindopril and indapamide in Bosnia and Herzegovina especially focusing on the treatment of unregulated essential hypertension. The results of this study indicate the risk for poor blood pressure control in patients with hypertension and diabetes mellitus. Thus, it is of significant importance for health workers in our country to raise awareness about existing diabetes mellitus as a frequent comorbidity with hypertension.

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Conflict of Interest: Aziz Šukalo, Jasna Džananović Jaganjac, Amna Tanović, Una Glamočlija, Meliha Mehić disclose the following relationships – they are employees of Bosnalijek d.d., a pharmaceutical company producing perindopril and indapamide -based products. Bosnalijek d.d. had a role in the design of the study, in the collection, analyses, and interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

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