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ORIGINAL PAPER

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Efficacy and Safety of Perindopril in Patients with Essential Hypertension

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ABSTRACT

Introduction: Perindopril is a tissue-specific ACE inhibitor with 24 hours long blood pressure-lowering effect, which protects blood vessels and decreases the variability of blood pressure. **Aim:** The aim of our study was to investigate the effectiveness and safety of perindopril in newly diagnosed or previously treated but uncontrolled adult hypertensive patients. **Methods:** This prospective cohort study included primary care patients with essential hypertension. Primary study outcomes were decreasing arterial blood pressure to normal levels (<140/90 mmHg), reducing systolic arterial blood pressure for 10 mmHg or more and reducing diastolic arterial blood pressure for 5 mmHg or more. Safety was evaluated by type and frequency of adverse events. **Results:** In the great majority of the study patients (more than 96%) perindopril was effective as monotherapy, achieving a significant reduction in both systolic and diastolic blood pressure, and in three-quarters of the study patients it normalized both systolic and diastolic blood pressure. The effectiveness of perindopril was shown in both patients with previously and newly diagnosed hypertension, adverse events were mild and rare, even hyperkalemia was encountered less often than before the onset of the therapy with perindopril. **Conclusions:** Our study confirmed excellent effectiveness of perindopril in the treatment of essential hypertension and its remarkable safety. When used as monotherapy of hypertension, perindopril's doses should be carefully titrated until the achievement of full effect, which in some patients should be awaited for at least 6 months from onset of the therapy.

Keywords: Perindopril, Essential hypertension, Effectiveness, Safety.

1. INTRODUCTION

Essential hypertension is still the most prevalent non-communicable disease all over the world; back in the year 2000 nothing less than 26.4% of the adult population globally had hypertension (1). Although true treatment-resistant hypertension is relatively rare (about 7.3% of all patients with hypertension), almost 35.6% of patients receive suboptimal treatment, and further 15.4% is not adherent, so optimal control of blood pressure is not achieved in every other patient (2). Starting optimal drug treatment of essential hypertension from the moment when hypertension was diagnosed or as early as possible during its course is associated with improved cardiovascular outcomes (3).

Angiotensin Converting Enzyme (ACE) inhibitors are frequently used as initial or early therapy of essential hypertension because their administration in clinical trials was associated with a decrease in cardiovascular morbidity and mortality (4). Perindopril stands out of the group of ACE inhibitors by its dose-dependent and long-lasting blood pressure-lowering effect, by the protection of blood vessels (improves endothelial function and decreases wall stiffness) and by a decrease in variability of blood pressure (5). After obtaining marketing authorization, perindopril's effectiveness and safety were studied in a few cohort studies which showed decreased all-cause and cardiovascular mortality or morbidity (e.g. worsening of renal function, cardiovascular diseases) in comparison with other ACE-inhibitors (6-8). However, perindopril was not compared with all of the ACE inhibitors available on the market, suggesting that further observational studies are necessary

to get a complete picture of perindopril's clinical utility.

2. AIM

The aim of our study was to investigate the effectiveness and safety of perindopril in newly diagnosed or previously treated but uncontrolled adult hypertensive patients.

3. METHODS

The cohort design was chosen for this observational study, conducted from September the 1st, 2018 to November the 30th, 2019 at ten primary care Health Centers in Bosnia & Herzegovina. The study subjects were enrolled if the following inclusion criteria had been met: outpatients, diagnosis of essential hypertension grade 1 according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension (blood pressure $\geq 140/90$ mmHg) (9), prescription of perindopril as mono- or add-on therapy and age between 30 and 75 years. The criteria for non-inclusion were: a history of angioneurotic edema, allergy to perindopril or adjuvant compounds, patients with treatment-resistant hypertension (after therapeutic trials with a combination of 3 antihypertensive drugs), the patients already treated with valsartan, fixed combination of valsartan/sacubitril or aliskiren, patients with mental disorders, severe co-morbidity (e.g. severe renal or liver failure), cancer and pregnancy. The patients were excluded from the study if the following happened: worsening of hypertension (translation from grade 1 to grade 2), serious adverse events and conception during the study period. The study was approved by the Drug Agency of Bosnia & Herzegovina.

Primary study outcomes were decreasing arterial blood pressure to target levels according to the 2018 ESC/ESH Guidelines ($<140/90$ mmHg), reducing systolic arterial blood pressure for 10 mmHg or more and reducing diastolic arterial blood pressure for 5 mmHg or more. Secondary study outcomes were the absolute value of arterial blood pressure at scheduled study visits and adverse events. Arterial blood pressure was measured at physician's office, under standardized conditions recommended for a valid measurement by the 2018 ESC/ESH Guidelines (9). The patients were followed for 12 months, blood pressure and heart rate were measured before prescribing perindopril, and 3, 6 and 9 months thereafter. On occasions when arterial blood pressure and heart rate were measured the following data were also collected: adherence to antihypertensive treatment, adverse events, body weight and height, habits (smoking, drinking alcohol, lifestyle), existence of diabetes mellitus, concomitant therapy and serum levels of potassium, creatinine and blood urea nitrogen (BUN).

In total 1255 patients were enrolled in our study, 801 with previously diagnosed, but uncontrolled hypertension, and 424 with newly diagnosed arterial hypertension. Sixty-one patients did not complete the study (lost to follow-up), and for the further 32 patients the data collected were incomplete.

Statistical analysis

The data were first described by measures of central tendency (mean and median) and variability (standard deviation and range). Normality of the data distribution was checked by the Kolmogorov-Smirnov test. The significance

of differences in values of continuous variables among the repeated measurements was tested by the Student's T-test for dependent samples and One-way analysis of variance (when data distribution was normal) or by Wilcoxon Signed Rank test and Friedman test (when data distribution was not normal). The differences in values of categorical variables (e.g. frequencies) were tested by Chi-square or Fisher's test. All calculations were performed by Statistical Package for Social Sciences (SPSS) software, version 23.0 for Windows.

4. RESULTS

The baseline characteristics of the study cohort are shown in Table 1. Average daily dose of perindopril, percent of patients on monotherapy or taking two or more antihypertensives, and dropouts at baseline, visit 1 and 2 are shown in Figure 1.

Effectiveness of perindopril in the whole study cohort is shown in Table 2, where for each study visit average systolic and diastolic arterial pressure, percent of patients achieving systolic normotension (<140 mmHg), percent of patients achieving diastolic normotension (<90 mmHg), percent of patients with a reduction of systolic pressure ≥ 10 mmHg, percent of patients with reduction of diastolic pressure ≥ 5 mmHg, and percent of patients achieving both systolic and diastolic normotension ($<140/90$ mmHg) are presented.

Effectiveness of perindopril in the subgroup of the study cohort with previously diagnosed hypertension ($n = 801$) is shown in Table 3, where for each study visit average systolic and diastolic arterial pressure, percent of patients achieving systolic normotension (<140 mmHg), percent of patients achieving diastolic normotension (<90 mmHg), percent of patients with reduction of systolic pressure ≥ 10 mmHg, percent of patients with a reduction of diastolic pressure

Variable	Value(s), mean \pm SD*
Age (years)	58.1 \pm 11.3
Sex (M/F) (No, %)	644(51.3%)/609 (48.5%)
Previously diagnosed arterial hypertension (No, %)	801 (65.5%)
Newly diagnosed arterial hypertension (No, %)	422 (34.5%)
Duration of hypertension (years)	10.6 \pm 10.1
Height (cm)	174.4 \pm 46.6
Weight (kg)	83.8 \pm 13.2
Waist circumference (cm)	98.2 \pm 15.3
Body Mass Index (kg/m ²)	28.6 \pm 10.8
Smokers (No, %)	496 (39.9%)
Ex-smokers (No, %)	216 (22.6%)
Number of cigarettes per day	17.8 \pm 11.1
Alcohol (No, %)	285 (23.2%)
Sedentary lifestyle (No, %)	723 (59.1%)
Diabetes mellitus (No, %)	297 (24.8%)
Type 2 (No, %)	287 (22.7%)
Type 1 (No, %)	10 (3.4%)
Duration of diabetes mellitus (years)	8.9 \pm 6.5

Table 1. Baseline characteristics of the study cohort ($n = 1255$). * standard deviation

	Baseline (n=1255)	Visit 1 (3 months from the baseline) (n=1249)	Visit 2 (6 months from the baseline) (n=1229)	Visit 3 (9 months from the baseline) (n=1194)	Δ baseline-Visit 3
Systolic blood pressure (mmHg)	159.9±13.8	144.5±23.2*	135.9±10.9*	131.7±9.0*	28.2±14.0*
Diastolic blood pressure (mmHg)	96.4±21.3	86.9±8.1*	83.0±24.4*	79.9±7.3*	16.8±22.3*
Percent of patients achieving systolic normotension (<140 mmHg)	0%	339 (27.1%)	697 (56.7%)	910 (76.6%)	76.6%
Percent of patients achieving diastolic normotension (<90 mmHg)	0%	618 (49.5%)	946 (77.0%)	1075 (90.5%)	90.5%
Percent of patients achieving both systolic and diastolic normotension (<140/90 mmHg)	0%	282 (22.6%)	646 (52.6%)	873 (73.5%)	73.5%
Percent of patients with reduction of systolic pressure \geq 10 mmHg	0%	1005 (80.5%)	1140 (92.8%)	1144 (96.3%)	96.3%
Percent of patients with reduction of diastolic pressure \geq 5 mmHg	0%	969 (77.6%)	1105 (89.9%)	1121 (96.4%)	96.4%

Table 2. Effectiveness of the perindopril shown for the whole study cohort. * significant difference from previous visit, $p < 0.001$

	Baseline (n=801)	Visit 1 (3 months from the baseline) (n=796)	Visit 2 (6 months from the baseline) (n=787)	Visit 3 (9 months from the baseline) (n=771)	Δ baseline-Visit 3
Systolic blood pressure (mmHg)	161.0±14.3	145.8±27.6*	136.4±10.8*	132.0±9.0*	29.1±14.8*
Diastolic blood pressure (mmHg)	97.1±16.2	87.2±8.3*	83.4±30.1*	79.7±6.9*	17.6±26.8*
Percent of patients achieving systolic normotension (<140 mmHg)	0%	184 (23.1%)	416 (52.9%)	570 (73.9%)	73.9%
Percent of patients achieving diastolic normotension (<90 mmHg)	0%	373 (46.9%)	595 (75.6%)	690 (89.5%)	89.5%
Percent of patients achieving both systolic and diastolic normotension (<140/90 mmHg)	0%	158 (19.8%)	395 (50.2%)	556 (72.1%)	72.1%
Percent of patients with reduction of systolic pressure \geq 10 mmHg	0%	639 (80.3%)	724 (92.0%)	731 (94.8%)	94.8%
Percent of patients with reduction of diastolic pressure \geq 5 mmHg	0%	599 (75.3%)	689 (87.5%)	712 (92.3%)	92.3%

Table 3. Effectiveness of the perindopril shown for the subgroup of the study cohort with previously diagnosed hypertension. * significant difference from previous visit, $p < 0.001$

\geq 5 mmHg, and percent of patients achieving both systolic and diastolic normotension (<140/90 mmHg) are presented.

Effectiveness of perindopril in the subgroup of the study cohort with newly diagnosed hypertension ($n = 424$) is shown in Table 4, where for each study visit average systolic and diastolic arterial pressure, percent of patients achieving systolic normotension (<140 mmHg), percent of patients achieving diastolic normotension (<90 mmHg), percent of patients with reduction of systolic pressure \geq 10 mmHg, percent of patients with reduction of diastolic pressure \geq 5 mmHg, and percent of patients achieving both systolic and diastolic normotension (<140/90 mmHg) are presented.

Serum levels of potassium, creatinine and BUN at baseline and the 3rd visit (9 months from enrollment) are shown in Table 5. During the study no serious adverse events were recorded; Table 6 shows all adverse events reported by the patients or noticed by the study investigators.

5. DISCUSSION

Perindopril in our study was very effective and safe antihypertensive drug; in great majority of the study patients

(more than 96%) it was effective as monotherapy, achieving significant reduction in both systolic and diastolic blood pressure, and in three-quarters of the study patients it normalized both systolic and diastolic blood pressure. The effectiveness of perindopril was preserved in both patients with previously and newly diagnosed hypertension, and adverse events were mild and rare, while hyperkalemia was encountered less often than before onset of the therapy with perindopril.

Excellent effectiveness of perindopril in achieving blood pressure control observed in our study was confirmed in a cohort study by Bansal and associates, who found that 71.1% of patients with stage 1 hypertension and average age of 45 years ($n = 426$) achieved complete blood pressure control with perindopril monotherapy (10) with or without its fixed dose combinations (FDC). In the same study safety of perindopril was remarkable, since dry cough that led to discontinuation of treatment was observed in only 0.1% of patients. Excellent safety profile of perindopril was also confirmed in our study, where over 99% of patients at the end of the study reported no adverse events, and dry

	Baseline (n=424)	Visit 1 (3 months from the baseline) (n=421)	Visit 2 (6 months from the baseline) (n=412)	Visit 3 (9 months from the baseline) (n=408)	$\Delta_{\text{baseline-Visit 3}}$
Systolic blood pressure (mmHg)	157.4±12.5*	141.0±11.8*	134.6±10.8*	131.0±8.7*	26.6±12.4*
Diastolic blood pressure (mmHg)	95.5±7.8*	86.5±7.6*	82.3±7.3*	80.1±8.0*	15.5±9.7*
Percent of patients achieving systolic normotension (<140 mmHg)	0%	158 (37.5%)	266 (64.6%)	328 (80.4%)	80.4%
Percent of patients achieving diastolic normotension (<90 mmHg)	0%	225 (53.4%)	330 (80.1%)	372 (91.2%)	91.2%
Percent of patients achieving both systolic and diastolic normotension (<140/90 mmHg)	0%	113 (26.8%)	234 (56.8%)	310 (76.0%)	76.0%
Percent of patients with reduction of systolic pressure ≥ 10 mmHg	0%	332 (78.9%)	383 (92.9%)	397 (97.3%)	97.3%
Percent of patients with reduction of diastolic pressure ≥ 5 mmHg	0%	346 (82.2%)	386 (93.7%)	394 (96.6%)	96.6%

Table 4. Effectiveness of the perindopril shown for the subgroup of the study cohort with newly diagnosed hypertension. * significant difference from previous visit, $p < 0.001$

	Baseline	Visit 3	$\Delta_{\text{baseline-Visit 3}}$	p
Potassium (mM/L)	4.61±4.5	4.47±3.2	-0.15±5.68	0.378
Hyperkalemia (≥ 5.0 mM/L)	163 (14.0%)	103 (9.1%)	-4.8%	<0.001
Creatinine (mM/L)	79.1±28.4	79.0±25.8	-1.29±12.1	0.001
BUN (mM/L)	7.5±9.8	8.5±11.8	0.67±10.4	0.18

Table 5. Serum levels of potassium, creatinine and BUN at baseline and at the 3rd visit (9 months from enrollment) for the whole study cohort.

	Visit 1 (3 months from the baseline) (n=1249)	Visit 2 (6 months from the baseline) (n=1229)	Visit 3 (9 months from the baseline) (n=1194)
No adverse events (No, %)	1219 (97.6%)	1215 (98.9%)	1191 (99.7%)
Cough (No, %)	13 (1.0%)	3 (0.2%)	3 (0.3%)
Headache (No, %)	9 (0.7%)	3 (0.2%)	–
Vertigo (No, %)	3 (0.2%)	1 (0.1%)	–
Increase in blood pressure (No, %)	2 (0.2%)	–	–
Nausea (No, %)	1 (0.1%)	1 (0.1%)	–
Fainting (No, %)	–	2 (0.2%)	–
Hair loss (No, %)	1 (0.1%)	–	–
Tinnitus (No, %)	–	1 (0.1%)	–
Rash (No, %)	1 (0.1%)	–	–
Dyspepsia (No, %)	–	1 (0.1%)	–
Hypotension (No, %)	–	1 (0.1%)	–
Weight loss (No, %)	–	1 (0.1%)	–

Table 6. Adverse events reported by the patients or spotted by the study investigators.

cough was reported in only 0,3% of patients. However, it is important to note that full effectiveness of perindopril could be expected after more than 6 months of treatment; in studies that followed the patients taking perindopril for shorter periods (e.g. two or three months) normalization of blood pressure was observed in 30.8% of cases (11)age, weight, baseline sitting and standing systolic and diastolic blood pressure. At 0, 4 and 8 weeks the mean SiDBP in the valsartan group were 101.4, 92.8 and 91.0 mmHg respectively. The corresponding BP for the perindopril treated group was 102.6, 93.8 and 93.2 mmHg. (95% CI -1.39 to +3.27, which underestimated benefits of the treatment. This

phenomenon was observed in our study, as normalization of blood pressure after three months of perindopril treatment was observed in only 22% of patients, but it reached prevalence as high as 73% after 9 months. It is also important to stress that more than 96% of patients in our study achieved reduction of systolic pressure ≥ 10 mmHg, and that of diastolic pressure ≥ 5 mmHg, which is very important if we take into consideration that every 10 mmHg reduction of systolic blood pressure is associated with significant reduction of macro and microvascular complication, target organ damage and longer survival.

Antihypertensive effect of perindopril is dose-depen-

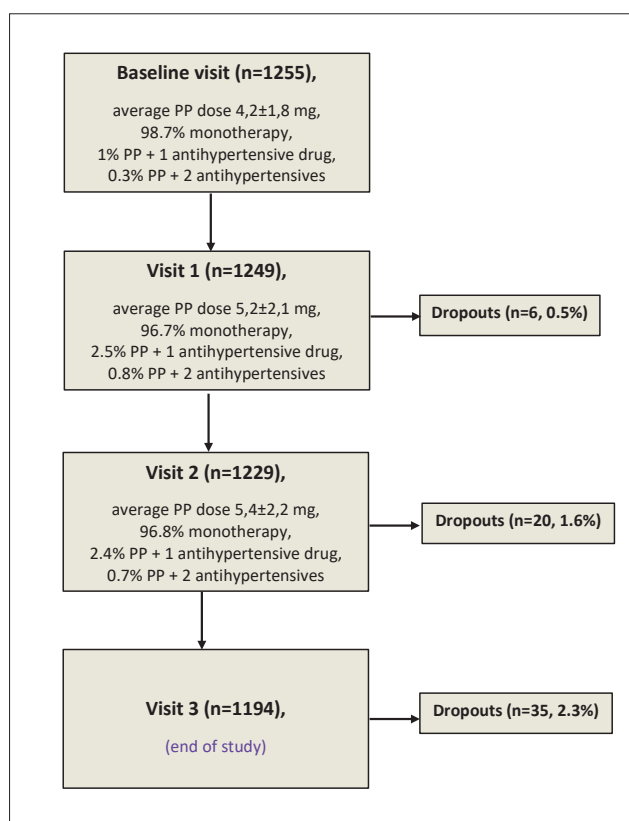


Figure 1. Doses of perindopril (PP) prescribed and dropouts recorded according to the study visit (visit 1 – 3 months from enrollment, visit 2 – 6 months from enrollment, visit 3 – 9 months from enrollment)

dent, and our patients reached maximum blood pressure reduction with higher average daily doses (5.4±2.2 mg). In large study of Tsoukas and associates (8298 patients) 8 mg of perindopril daily resulted with additional blood pressure reduction on average 10.1/5.3 mmHg, when compared with effects of 4 mg daily dose (12). The PREFER study on 824 primary care patients with uncontrolled hypertension demonstrated high, dose-dependent effectiveness of perindopril, since normalization of blood pressure was achieved in 48.1% of patients after titration of perindopril daily dose from 5 to 10 mg (13). It is interesting that in PREFER study perindopril succeeded to normalize blood pressure in patients whose hypertension was not controlled with other ACE inhibitors.

Although perindopril has clear effectiveness in regard to the blood pressure control, there are additional benefits of its use in hypertensive patients with other cardiovascular comorbidities that cannot be explained only by blood pressure reduction (14). Perindopril is effective in secondary prevention of coronary disease (risk of cardiovascular death or myocardial infarction is relatively reduced for 20%) (15), it causes regression of left ventricular hypertrophy, decreases level of plasma brain natriuretic peptide and decreases stiffness of aortic wall (16). In large European PROTECT trials (n = 800) it was shown that perindopril contributes to decreasing in intima/media thickness of the arterial wall, slowing in this way development of atherosclerosis (17). This additional protective effects of perindopril inspired some experts to recommend perindopril as „a first-line therapeutic agent in hypertension, heart failure and acute

myocardial infarction and a tool of secondary prevention of coronary artery disease“ (18).

Main limitation of our study was lack of control cohort, composed of patients with essential hypertension taking some other ACE inhibitor as monotherapy; such comparison would enable more precise estimate of perindopril's effectiveness and safety, and adjustment for other factors influencing blood pressure control. Besides, more relevant laboratory parameters that either influence blood pressure or could be an adverse drug reaction should have been followed, like blood count, proteinuria, serum level of cholesterol, etc.

6. CONCLUSION

Our study confirmed excellent effectiveness of perindopril in treatment of stage 1 essential hypertension, and its remarkable safety. When used as monotherapy of hypertension, perindopril's doses should be carefully titrated until achievement of full effect, which in some patients should be awaited for at least 6 months from onset of the therapy.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** E.H, E.B. and A.Dz. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. R.A.A., E.B., A.I and S.M. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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