Official journal of
Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

2014, Vol 21, 63-69
DOI 10.1007/s40292-013-0036-x

High Blood Pressure & Cardiovascular Prevention

Efficacy of Single-Pill Perindopril/Indapamide in Patients with Hypertension and Type 2 Diabetes

T. A. Netchessova • A. P. Shepelkevich •
T. V. Gorbat • on behalf of the NIKA Study Group

Adis

High Blood Press Cardiovasc Prev (2014) 21:63–69
DOI 10.1007/s40292-013-0036-x

ORIGINAL ARTICLE

Efficacy of Single-Pill Perindopril/Indapamide in Patients with Hypertension and Type 2 Diabetes

T. A. Netchessova · A. P. Shepelkevich · T. V. Gorbat · on behalf of the NIKA Study Group

Received: 9 October 2013 / Accepted: 4 December 2013 / Published online: 20 December 2013

Abstract

Objective Hypertension and type 2 diabetes in combination are associated with a significantly higher level of cardiovascular events. The aim of this prospective study was to evaluate the antihypertensive efficacy and tolerability of single-pill perindopril/indapamide in patients with hypertension and type 2 diabetes.

Design and Methods Patients with both hypertension and type 2 diabetes were enrolled in this multicenter, prospective, open clinical study. Single-pill perindopril/indapamide was either prescribed on its own (started or switched to from previous treatment) or added to previous therapy. Perindopril/indapamide dosage could be increased, from 5/1.25 mg to 10/2.5 mg once daily, if blood pressure (BP) was uncontrolled. BP and tolerability were assessed at 4 visits over a 6-month period. Microalbuminuria was assessed at baseline and 6 months in a subgroup.

Results 397 patients were analyzed (age 57.6 ± 9.4 years, men 46 %). At baseline, systolic blood pressure (SBP) was 160.0 ± 14.3 mmHg, diastolic blood pressure (DBP) 95.2 ± 8.3 mmHg, and pulse pressure 64.8 ± 12.7 mmHg. Nearly half (45 %) of patients received perindopril/indapamide alone and 55 % added this single-pill combination to existing therapy. After 6 months, SBP fell by 30 mmHg, DBP by 14 mmHg, and pulse pressure by 16 mmHg (all $p < 0.0001$). SBP was normalized (<140 mmHg) in 84 % of patients who took perindopril/indapamide 5/1.25 mg alone and in 90 % of patients who took perindopril/indapamide 10/2.5 mg alone. Tolerability was rated "good" or "better" by nearly all (99 %) patients. In a microalbuminuria subgroup ($n = 59$; baseline microalbuminuria 20–200 mg/L; average age 60.5 ± 11.5 years; 28 men [47 %]), there was a significant decrease in SBP (from 160.5 ± 13.9 mmHg to 132.6 ± 12.0 mmHg) and DBP (from 95.3 ± 7.8 mmHg to 81.6 ± 8.4 mmHg) ($p < 0.001$). Target SBP was reached by 71 % of these patients. Microalbuminuria decreased in 75 % of the subgroup during the follow-up period; levels fell significantly from 45 mg/L (30–88 mg/L) to 30 mg/L (20–50 mg/L) ($p < 0.0001$).

Conclusion Treatment with single-pill perindopril/indapamide 5/1.25 or 10/2.5 mg significantly reduced BP, improved BP control, and enhanced kidney protection in patients with hypertension and type 2 diabetes in everyday clinical practice.

Keywords Perindopril · Indapamide · Hypertension · Type 2 diabetes · Microalbuminuria · Nephroprotection

1 Introduction

The combination of arterial hypertension and type 2 diabetes is the main reason for the early disability and mortality of patients from cardiovascular complications [1, 2]. Patients with type 2 diabetes are at greater risk of cardiovascular complications than the general population and, when coupled with hypertension, risk increases an additional two- to three-fold [3]. Correction of blood pressure (BP) in patients with type 2 diabetes is unsatisfactory [4, 5]. The latest European guidelines recommend that

T. A. Netchessova (✉) · T. V. Gorbat
Republican Scientific Practical Center "Cardiology",
R. Luxembourg str. 110, Minsk, Belarus
e-mail: nechesova@tut.by

A. P. Shepelkevich
Belarusian State Medical University, Minsk, Belarus

antihypertensive therapy be initiated in patients with diabetes when systolic blood pressure (SBP) ≥140 mmHg and that combination therapy should be prioritized [6]. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, and calcium channels blockers (CCB) are the current agents of choice for antihypertensive therapy in patients with type 2 diabetes.

Nephroprotection is important in patients with type 2 diabetes as reduced renal function with albuminuria and reduced estimated glomerular filtration rate (GFR) are independent risk factors for cardiovascular and renal outcomes [7, 8]. ACE inhibitors have been shown to exert nephroprotective and vasoprotective effects, decrease insulin resistance, modulate endothelial function, and have no deleterious effect on purine or lipid exchange [9, 10]. Thiazide-like diuretics may reverse or delay the progress of diabetic nephropathy as well as lower BP without adversely affecting metabolism, an important consideration in diabetes [11].

The largest phase 3 hypertension trial in patients with type 2 diabetes, ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), showed that the combination of perindopril and indapamide lessens the risk of mortality and risk of coronary and renal complications [12]. NIKA (NolIprel forte A as the Key therapy for diabetic pAtients with hypertension) was designed to study the antihypertensive efficacy and tolerability of single-pill perindopril/indapamide in patients with arterial hypertension and type 2 diabetes in daily clinical practice.

2 Material and Methods

NIKA was an open, non-comparable, prospective study with dose titration. Patients were included if they had hypertension and type 2 diabetes with baseline BP ≥140/90 mmHg. Exclusion criteria included age <18 years, concomitant renal or hepatic failure, known hypersensitivity to ACE inhibitors or indapamide, and contraindications to treatment. Patients with untreated heart failure and women of reproductive age who were planning to become pregnant were not included. Recruitment took place from November 18, 2009, to January 18, 2010. All patients gave their written informed consent. NIKA was conducted in accordance with The Declaration of Helsinki and its revisions and was approved by all local ethics committees involved. Thirty-four cardiologists and twenty-two endocrinologists participated in the program.

The research program consisted of two phases: a screening phase, which lasted 30 days, followed by an active antihypertensive treatment phase, which lasted 6 months. In antihypertensive treatment-naive patients with hypertension and type 2 diabetes, treatment was initiated with single-pill perindopril/indapamide 5/1.25 mg. In patients whose BP was uncontrolled with previous antihypertensive therapy, patients were either switched to perindopril/indapamide 5/1.25 mg from their previous therapy or perindopril/indapamide 5/1.25 mg was added to existing antihypertensive treatment (calcium channel blockers or beta-blockers, not diuretics and/or renin-angiotensin-aldosterone system [RAAS] inhibitors as these were excluded), if the doctor wished. After one month, perindopril/indapamide could be uptitrated to perindopril/indapamide 10/2.5 mg, according to BP response (<140/90 mmHg).

At each visit, sitting BP, standing BP (for the detection of orthostatic hypotension), and heart rate were measured. Blood pressure measurement was carried out in accordance with the 2007 European Society of Hypertension/European Society of Cardiology practice guidelines for the management of arterial hypertension [13]. Cardiovascular risk factors, electrocardiograms, lipid profile, fasting blood glucose, glycosylated hemoglobin, creatinine, and blood potassium were evaluated twice; once during the screening phase and again after 6 months. All side effects were reported in an adverse reaction report. Treatment tolerability was assessed. Urinalysis was used to detect proteinuria and microalbuminuria, the presence of which confirms not only early kidney involvement, but also reflects the general condition of the microcirculation [14]. Microalbuminuria was assessed at baseline and after 6 months in a subgroup of patients using an immunoturbidimetric method with an Olympus analyzer (Olympus Diagnostic Systems Group, Tokyo, Japan) and a morning urine sample. GFR was calculated using the Cockcroft-Gault formula [14]. The effectiveness of nephroprotection was analyzed in relation to baseline BP level, presence of concomitant microvascular complications, and a selected regimen of antihypertensive treatment.

The following endpoints were assessed: mean SBP decrease at 1, 3, and 6 months and mean DBP and pulse pressure decrease after 6 months in the total population; mean BP decrease after 6 months with different single-pill perindopril/indapamide treatment strategies; BP control in the total population at study end, i.e., the percentage of the patients who reached target BP level (<140/90 mmHg); the percentage of patients who reached target BP level with different treatment regimens; treatment tolerability, according to doctors and patients; and the percentage of patients with treatment side effects leading to treatment discontinuation. Microalbuminuria was also assessed at baseline and after 6 months of therapy in a subgroup of patients.

Data are presented as mean ± standard deviation (SD), number and percentage, or median (first quartile–third quartile). Statistical analyses were performed on an

intention-to-treat basis. A Shapiro–Wilk test was used to examine whether variables were normally distributed. Comparison of two dependent samples was evaluated by pairwise Student's criterion, and matching pairs Wilcoxon test. In order to determine the factors that influenced changes in albuminuria over time, a stepwise regression analysis was conducted, with SBP, DBP, body mass index, waist measurement, triglycerides, total cholesterol, high-density lipoproteins, low-density lipoproteins, and fasting blood glucose as independent parameters. Results were considered significant if $p < 0.05$. Statistical analysis was performed using Biostat 2007 (AnalystSoft Inc., Alexandria, VA, USA) and StatPlus 2009 (AnalystSoft Inc., Alexandria, VA, USA) software.

3 Results

A description of patients and cardiovascular risk factors is shown in Table 1. A small minority of the 422 patients included (n = 25 [6 %]) were not seen at all 4 visits and were excluded from the analysis. The remaining 397 patients (181 men and 216 women [94 %]) were relatively young (under 60 years), were most likely to have stage 2 hypertension, and to have had diabetes for less than 5 years. Over two thirds were obese. A third or more had diabetic retinopathy, angina pectoris, or chronic heart failure. Baseline antihypertensive treatments are also shown in Table 1. At inclusion, most (89 %) patients were receiving antihypertensive treatment. Perindopril/indapamide was prescribed alone (started or switched from previous treatment) in 45 %, and added to previous therapy in the rest. It should be noted that lipid-lowering therapy was uncommon, as it was used by 13 % at baseline and 14 % after 6 months.

3.1 Efficacy

At the end of the study, 42 % (n = 167) of patients were being treated with single-pill perindopril/indapamide 5/1.25 mg alone, 3 % (n = 10) with single-pill perindopril/indapamide 10/2.5 mg alone, and 55 % (n = 220) with perindopril/indapamide 5/1.25 mg (49 %, n = 195) or 10/2.5 mg (6 %, n = 25) in combination with other antihypertensive drugs. In the total population, mean SBP decreased by 19.5 ± 12.2 mmHg, 25.6 ± 13.9 mmHg, and 30.0 ± 14.0 mmHg after 1, 3, and 6 months of treatment, respectively (all $p < 0.0001$ versus baseline). After 6 months of treatment, mean SBP had decreased significantly from 160.0 ± 14.3 mmHg to 130.0 ± 9.3 mmHg, mean DBP from 95.2 ± 8.3 mmHg to 81.3 ± 6.3 mmHg, and mean pulse pressure from 64.8 ± 12.7 to 48.7 ± 8.0 mmHg (all $p < 0.0001$).

In the group on perindopril/indapamide 5/1.25 mg alone, mean SBP decreased by 27.7 ± 13.5 mmHg, from 156.4 ± 13.1 to 128.8 ± 7.8 mmHg, while mean DBP decreased by 13.4 ± 9.2 mmHg, from 94.3 ± 8.0 to 80.9 ± 6.0 mmHg, after 6 months (both $p < 0.0001$). In the group on perindopril/indapamide 10/2.5 mg alone, mean SBP decreased by 42.5 ± 14.4 mmHg, from 170.0 ± 13.5 to 127.5 ± 8.2 mmHg; while mean DBP decreased by 20.1 ± 7.6 mmHg, from 98.5 ± 8.2 to 78.4 ± 5.2 mmHg, after 6 months (both $p < 0.0001$). When single-pill perindopril/indapamide was combined with another antihypertensive, mean SBP decreased by 31.2 ± 14.0 mmHg, from 162.3 ± 14.6 to 131.1 ± 10.3 mmHg, while mean DBP decreased by 14.0 ± 9.2 mmHg, from 95.7 ± 8.5 to 81.7 ± 6.5 mmHg, after 6 months (both $p < 0.0001$).

In the total population, 79 % of patients reached the target SBP < 140 mmHg and 85 % reached the target DBP < 90 mmHg. With perindopril/indapamide, target SBP was reached by 86 % of untreated patients, 84 % of those switched from previous treatment, and 74 % of those to whom this was added to previous treatment. The highest percentage of patients who achieved target SBP and DBP levels was in the group of patients who received perindopril/indapamide 10/2.5 mg (90 %). Of the patients who received perindopril/indapamide 5/1.25 mg alone, 84 % reached target SBP and 86 % reached target DBP (Fig. 1). Our results also indicate that perindopril/indapamide is metabolically neutral (Table 2).

3.2 Tolerability

Doctors assessed treatment tolerability as "good" or "very good" in 99 % of patients, while 98 % of patients evaluated tolerability as "good" or "very good." Of the 20 patients (5 %) who refused to continue treatment, 2 % refused due to side effects, 2 % for financial reasons, <1 % felt unwell when BP was normalized, and <1 % had medication withdrawn after visiting other doctors. Allergic reactions were detected in 2 %, nausea in <1 %, and cough in <1 %. No serious or unexpected side effects occurred during the study. Six patients (1 %) refused further medical observation. Patient compliance was satisfactory.

3.3 Microalbuminuria Subanalysis

Microalbuminuria was reviewed separately, and of 155 patients assessed at baseline, 59 (mean age 60.5 ± 11.5 years, 28 [47 %] men) had microalbuminuria (range of 20 to 200 mg/L). In this subgroup of 59, there was a significant decrease in mean SBP (from 160.5 ± 13.9 mmHg to 132.6 ± 12.0 mmHg) ($p < 0.001$), mean DBP (from 95.3 ± 7.8 to 81.6 ± 8.4 mmHg), and pulse pressure (from 65.1 ± 11.3 to 51.0 ± 9.1 mmHg)

Table 1 Baseline characteristics (N = 397), risk factors and previous antihypertensive medication. Values are means ± standard deviations or numbers and percentages. BMI, body mass index; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure

Characteristic	Value (N = 397)	Characteristic	Data available, (n)	Risk factors (n)	Value
Demographics		Waist measurement (cm)	392 (99 %)	361 (92 %)	104.4 ± 13.6
Age (years)	57.6 ± 9.4	Body mass index (kg/m^2)	397 (100 %)	380 (96 %)	32.7 ± 5.1
Men	181 (46 %)	*Blood glucose/lipids and kidney function*			
Smoking	53 (13 %)	Fasting blood sugar (mmol/L)	397 (100 %)	397 (100 %)	7.7 ± 2.0
Vital statistics		Glycated hemoglobin, HbA_{1c} (%)	207 (52 %)	140 (68 %)	7.1 ± 0.1
Systolic blood pressure (mmHg)	160.0 ± 14.3	Total cholesterol (mmol/L)	397 (100 %)	340 (86 %)	6.1 ± 1.2
Diastolic blood pressure (mmHg)	95.2 ± 8.3	Triglycerides (mmol/L)	392 (99 %)	278 (71 %)	2.2 ± 1.1
Pulse pressure (mmHg)	64.8 ± 12.7	Low-density lipoproteins (mmol/L)	277 (70 %)	196 (71 %)	3.5 ± 1.1
Heart rate (bpm)	76.7 ± 8.6	High-density lipoproteins (mmol/L)	307 (77 %)	126 (41 %)	1.3 ± 0.6
*Severity of hypertension**		Creatinine (μmol/L)	383 (96 %)	83 (22 %)	89.6 ± 19.8
Grade 1 (mild)	172 (43 %)	Microalbuminuria (mg/L)	155 (39 %)	59 (38 %)	63.9 ± 45.5
Grade 2 (moderate)	177 (45 %)	Proteinuria (mg/L)	304 (77 %)	57 (19 %)	0.03 ± 0.1
Grade 3 (severe)	48 (12 %)				

Characteristic	Value (N = 397)	Antihypertensive medication	Patients (%)	Dose (mg/day)
Duration of diabetes				
≤5 years	254 (64 %)	Enalapril	124 (31 %)	18.7 ± 12.2
>5 years to ≤10 years	103 (26 %)	Lisinopril	94 (24 %)	16.1 ± 9.0
>10 years to ≤15 years	24 (6 %)	Ramipril	20 (5 %)	5.8 ± 2.8
>15 years	16 (4 %)	Perindopril	18 (5 %)	4.3 ± 1.2
Weight†		Fosinopril	14 (4 %)	20.0 ± 0.0
Normal weight	17 (4 %)	Captopril	10 (3 %)	50.0 ± 17.7
Overweight	110 (28 %)	Quinapril	2 (<1 %)	10.0 ± 0.0
Grade 1 (mild) obesity	157 (40 %)	Eprosartan	4 (1 %)	600.0 ± 0.0
Grade 2 (moderate) obesity	84 (21 %)	Bisoprolol	103 (26 %)	5.8 ± 2.4
Grade 3 (severe) obesity	29 (7 %)	Metoprolol	34 (9 %)	67.3 ± 34.4
Comorbidities		Carvedilol	6 (2 %)	12.5 ± 0.0
Angina pectoris	136 (34 %)	Nebivolol	6 (2 %)	5.0 ± 0.0
Myocardial infarction	46 (12 %)	Atenolol	4 (1 %)	50.0 ± 0.0
Stroke/transient ischemic attack	18 (5 %)	Propranolol	1 (<1 %)	5.0 ± 0.0
Chronic heart failure	129 (33 %)	Amlodipine	82 (21 %)	6.9 ± 2.6
Diabetic retinopathy	194 (49 %)	Diltiazem	5 (1 %)	180.0 ± 0.0
Diabetic angiopathy	115 (29 %)	HCTZ	34 (9 %)	20.0 ± 6.5
		Indapamide 2.5 mg	61 (15 %)	2.9 ± 0.9
		Indapamide 1.5 mg	13 (3 %)	1.5 ± 0.0
		Furosemide	8 (2 %)	36.7 ± 8.2
		Torasemide	1 (<1 %)	5.0 ± 0.0
		Amlodipine/lisinopril 5/10 mg	13 (3 %)	–
		Enalapril/HCTZ 10/12.5 mg	16 (4 %)	–
		Captopril/HCTZ 50/25 mg	1 (<1 %)	–

* Mild hypertension (grade 1)—SBP 140–159 mmHg and/or DBP 90–99 mmHg; Moderate hypertension (grade 2)—SBP 160–179 mmHg and/or DBP 100–109 mmHg; and Severe hypertension (grade 3)—SBP ≥180 mmHg and/or DBP ≥110 mmHg

† BMI <25 kg/m^2 indicates normal weight; ≥25 to <30 kg/m^2, overweight; ≥30 to <35 kg/m^2, grade 1 obesity; ≥35 to <40 kg/m^2, grade 2 obesity; and ≥40 kg/m^2, grade 3 obesity

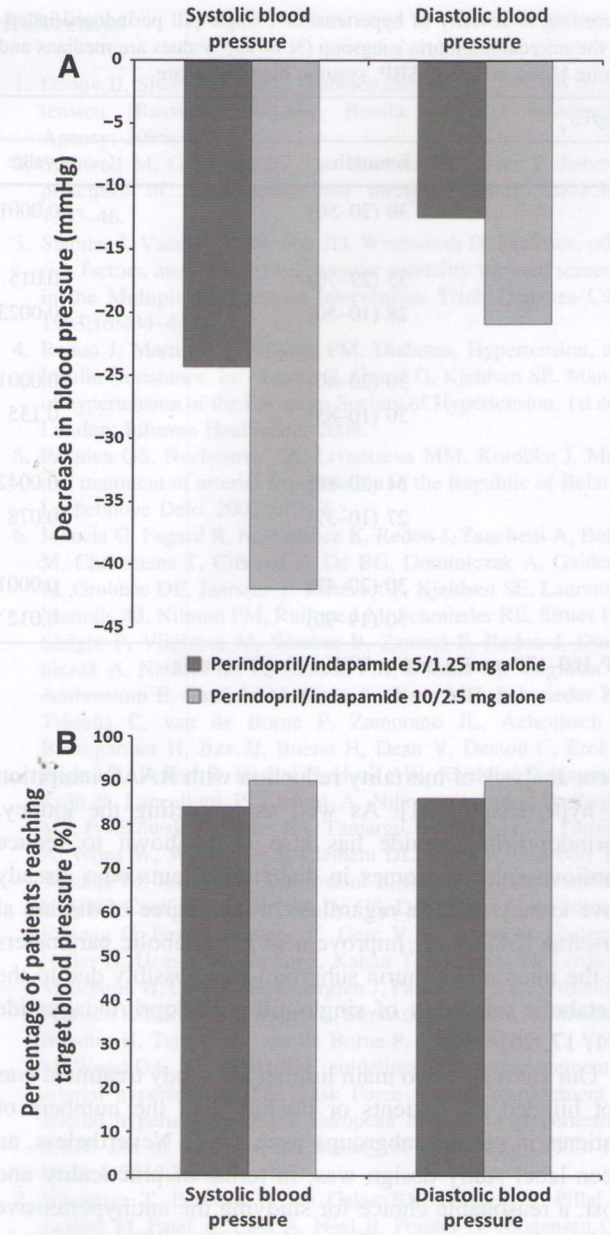

Fig. 1 **a** Systolic and diastolic blood pressure reduction after 6 months in patients treated with single-pill perindopril/indapamide alone (5/1.25 or 10/2.5 mg) and (**b**) the percentage of these patients who reached target systolic and diastolic blood pressure

after 6 months. Median plasma creatinine levels remained stable (87 [74–103] versus 87 [76–97] μmol/L at baseline and 6 months, respectively [p = 0.21]). Target SBP and DBP was achieved in over two-thirds (in 71 and 76 %, respectively).

Levels of microalbuminuria decreased with treatment, regardless of the severity of hypertension or chronic kidney disease, perindopril/indapamide dosage, or presence of diabetic complications (Table 3). Normoalbuminuria (<20 mg/L) was observed in 14 patients (24 %) after

Table 2 Metabolic parameters at baseline and after 6 months in the microalbuminuria subgroup (N = 59). Values are percentages or mean ± standard deviation in patients with available data. GFR, glomerular filtration rate

Metabolic parameter	Baseline	6 months
Fasting glycemia (mmol/L)	7.7 ± 2.0	6.1 ± 1.1
Total cholesterol (mmol/L)	6.1 ± 1.2	5.3 ± 0.8
Triglycerides (mmol/L)	2.2 ± 1.1	1.8 ± 0.7
Low-density lipoproteins (mmol/L)	3.5 ± 1.1	3.1 ± 1.0
High-density lipoproteins (mmol/L)	1.3 ± 0.6	1.4 ± 0.5

6 months of treatment, while there was a reduction of microalbuminuria in 30 (51 %) patients, from a mean of 58 mg/L (40–100 mg/L) to 34 mg/L (30–54 mg/L) ($p < 0.0001$). Significant linear dependence between baseline fasting blood glucose and changes in albuminuria over time ($F = 10.85$; $p = 0.0017$) was found.

A significant decrease in BP was observed in the 15 (25 %) patients in whom no decrease in albuminuria was noted. Reduction of albuminuria was observed in all groups, but was significant in the groups that received perindopril/indapamide 5/1.25 mg or perindopril/indapamide 10/2.5 mg alone. Kidney function, as measured by GFR, also improved with treatment. After 6 months, the percentage of patients with renal impairment (GFR <90 mL/min) decreased from 45 to 36 %.

4 Discussion

NIKA assessed the antihypertensive efficacy of single-pill perindopril/indapamide in the everyday clinical practice of cardiologists and endocrinologists. Treatment of patients with both hypertension and type 2 diabetes with single-pill perindopril/indapamide, either alone or added to previous therapy, resulted in significant reductions in SBP, DBP, and pulse pressure. Elevated SBP and DBP were normalized in most patients. Perindopril/indapamide also significantly reduced microalbuminuria and stopped the progression of chronic kidney disease. Our findings confirm that perindopril/indapamide provides renal protection and effectively lowers BP in mildly or moderately hypertensive patients with risk factors [15–17].

The antihypertensive efficacy of perindopril/indapamide in type 2 diabetes has been established in a phase 3 randomized controlled trial featuring 11,140 patients [12]. This efficacy was also witnessed in NIKA, as well as a clear dose-response relationship for BP reduction (Fig. 1). Elevated BP has been shown to be an important risk factor for determining the development and progression of nephropathy in patients with type 2 diabetes [18]. RAAS inhibitors reduce BP and protect the kidney, either as

Table 3 Changes in microalbuminuria level from baseline to 6 months, according to severity of hypertension*, single-pill perindopril/indapamide dosage, diabetic complication, and stage of chronic kidney disease† in the microalbuminuria subgroup (N = 59). Values are medians and interquartile range (in brackets). GFR, glomerular filtration rate; DBP, diastolic blood pressure; SBP, systolic blood pressure

	Albuminuria (mg/L)		
	Baseline	6 months	p-value
Total	45 (30–88)	30 (20–50)	<0.0001
*Grade of hypertension**			
Grade 1 (mild hypertension)	50 (40–145)	35 (29–70)	0.015
Grade 2 (moderate hypertension)	38 (30–76)	28 (10–50)	0.0023
Chronic kidney disease†			
Stage 1 (normal renal function)	40 (30–88)	30 (20–40)	<0.0001
Stage 2 (mild renal impairment)	47 (34–83)	30 (10–85)	0.135
Diabetic complication			
Retinopathy and/or angiopathy	49 (30–113)	34 (20–80)	0.0042
Retinopathy and angiopathy	40 (30–76)	27 (10–37)	0.078
Dosage of perindopril/indapamide			
Single-pill 5/1.25 mg alone	50 (33–88)	30 (20–47)	0.0001
Single-pill 10/2.5 mg alone	45 (30–87)	30 (19–90)	0.012

* Grade 1—SBP 140–159 mmHg and/or DBP 90–99 mmHg; grade 2—SBP 160–179 mmHg and/or DBP 100–109 mmHg

† Stage 1, GFR ≥90 mL/min; stage 2, 60 ≤ GFR < 90 mL/min

monotherapy or in combination therapy [19], as do thiazide-like diuretics [11, 20]. Given the wide choice of RAAS inhibitors, it is worth pointing out that current evidence favors ACE inhibitors over angiotensin receptor blockers for reducing mortality in hypertension [21].

European guidelines on hypertension management have underlined the efficacy of RAAS inhibitors in hypertensive patients with nephropathy, particularly RAAS inhibitors in combination with a different class of antihypertensive agent [6]. Nephroprotection was observed in NIKA. Perindopril/indapamide reduced microalbuminuria—irrespective of BP level or concomitant microvascular complications—and stopped the progression of chronic kidney disease in the microalbuminuria subgroup. This is important as recent reports indicate that even with permanent suppression of the RAAS, albuminuria remains a powerful predictor of cardiovascular events [22].

For this reason, simultaneous BP reduction and nephroprotection may be a useful management strategy in hypertensive patients with type 2 diabetes, even though not all evidence shows that a reduction of proteinuria leads to a reduction in cardiovascular outcomes [6]. An analysis by Garcia-Donaire and co-workers did, however, state that combination perindopril/indapamide in ADVANCE was "the only treatment providing primary and secondary prevention of renal events together with significant benefits in terms of all-cause and cardiovascular mortality, relative to a control group including RAAS inhibitors" [23]. The usefulness of perindopril for reducing all-cause and cardiovascular mortality was also recently confirmed by a meta-analysis of mortality reduction with RAAS inhibition in hypertension [21]. As well as protecting the kidney, perindopril/indapamide has also been shown to reduce cardiovascular outcomes in diabetic patients who already have kidney disease, regardless of the degree of disease at baseline [24]. A net improvement in metabolic parameters in the microalbuminuria subgroup was possibly due to the metabolic neutrality of single-pill perindopril/indapamide [11, 17, 25].

Our study had two main limitations: study treatment was not blinded for patients or doctors, and the numbers of patients in certain subgroups were small. Nevertheless, an open-label study design was, in terms of practicality and cost, a reasonable choice for studying the antihypertensive and nephroprotective effects of perindopril/indapamide in clinical practice. Second, the small patient numbers in the perindopril/indapamide 10/2.5 mg subgroups meant it was difficult to draw firm conclusions about this dosage. Even so, our findings give a good indication of the treatment benefits of the 10/2.5 mg dosage, and are line with those published elsewhere [17].

5 Conclusion

In patients with hypertension and type 2 diabetes in everyday clinical practice, treatment with single-pill perindopril/indapamide 5/1.25 or 10/2.5 mg significantly reduced BP, improved BP control, and enhanced kidney protection.

References

1. Dedov II, Shestakova MV. Diabetes mellitus and arterial hypertension [Russian]. Moscow, Russia: Medical Information Agency; 2006;344.
2. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365: 1333–46.
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16:434–44.
4. Redon J, Martinez F, Nilsson PM. Diabetes, Hypertension, and Insulin Resistance. In: Mancia G, Grassi G, Kjeldsen SE. Manual of hypertension of the European Society of Hypertension. 1st edn. London: Informa Healthcare; 2008.
5. Pavlova OS, Nechesova TA, Liventseva MM, Korobko I. Medical treatment of arterial hypertension in the Republic of Belarus. Lechebnoye Delo. 2008;3:23–7.
6. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De BG, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De BM, De GS, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159–219.
7. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, MacMahon S, Chalmers J. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009;20:1813–21.
8. Ruilope LM, Bakris GL. Renal function and target organ damage in hypertension. Eur Heart J. 2011;32:1599–604.
9. Tkacheva ON, Barabashkina AV, Novikova IM, Runikhina NK. The study of effects of ramipril and amlodipine combination in patients with arterial hypertension and type 2 diabetes mellitus. Kardiologiia. 2009;49:40–7.
10. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317:703–13.
11. Waeber B, Rotaru C, Feihl F. Position of indapamide, a diuretic with vasorelaxant activities, in antihypertensive therapy. Expert Opin Pharmacother. 2012;13:1515–26.
12. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829–40.
13. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the management of arterial hypertension. J Hypertens. 2007;25: 1751–62.
14. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43:S1–290.
15. Nechesova TA, Mitkovskaya NP, Lachimova TI, Lollini VA, Statkevich FM, Dolgoshei TS, Zhdanov AA. Treatment of ambulatory arterial hypertension with a fixed low-dose combination of perindopril/amlodipine: the NOTA study—Noliprel as a first-choice treatment in arterial hypertension. Lechebnoye Delo. 2008;1:12–6.
16. Ruilope LM, Segura J. Kidney protection: a key target in the management of patients with diabetes. J Hypertens Suppl. 2009;27:S15–8.
17. Pella D. Efficacy and safety of treatment of hypertensive patients with fixed combination perindopril/indapamide up to 10/2.5 mg: results of the FALCO FORTE programme. High Blood Press Cardiovasc Prev. 2011;18:107–13.
18. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24:302–8.
19. Leoncini G, Viazzi F, Pontremoli R. RAAS inhibition and renal protection. Curr Pharm Des. 2012;18:971–80.
20. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–98.
21. Ferrari R, Boersma E. The impact of ACE inhbition on all-cause and cardiovascular mortality in contemporary hypertension trials: a review. Expert Rev Cardiovasc Ther. 2013;11:705–17.
22. Cerezo C, Ruilope LM, Segura J, Garcia-Donaire JA, de la Cruz JJ, Banegas JR, Waeber B, Rabelink TJ, Messerli FH. Microalbuminuria breakthrough under chronic renin-angiotensin-aldosterone system suppression. J Hypertens. 2012;30:204–9.
23. Garcia-Donaire JA, Segura J, Cerezo C, Ruilope LM. A review of renal, cardiovascular and mortality endpoints in antihypertensive trials in diabetic patients. Blood Press. 2011;20:322–34.
24. Heerspink HJ, Ninomiya T, Perkovic V, Woodward M, Zoungas S, Cass A, Cooper M, Grobbee DE, Mancia G, Mogensen CE, Neal B, Chalmers J. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. Eur Heart J. 2010;31:2888–96.
25. Farsang C. Blood pressure and metabolic efficacy of fixed-dose combination of perindopril and indapamide in everyday practice. Blood Press. 2013;22(Suppl 1):3–10.