

# Antihypertensive Efficacy of Triple Combination Perindopril/Indapamide Plus Amlodipine in High-Risk Hypertensives: Results of the PIANIST Study (Perindopril-Indapamide plus Amlodipine in high risk hypertensive patients)

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## Abstract

**Objective** Our objective was to evaluate a triple-drug antihypertensive strategy for blood pressure control in patients with difficult-to-treat hypertension.

**Design** The Perindopril-Indapamide plus Amlodipine in high risk hypertensive patients (PIANIST) trial was an observational, 4-month, open-label study.

**Patients and interventions** A total of 4,731 patients at high or very high cardiovascular risk with hypertension that was not properly controlled despite antihypertensive therapy, and for whom study treatment (fixed-dose perindopril 10 mg/indapamide 2.5 mg + amlodipine 5 or 10 mg) was consistent with their existing therapeutic plan, were included.

**Outcomes** One-sample *t* tests and Chi-squared tests were performed to evaluate changes in blood pressure.

**Results** Mean baseline office blood pressure (OBP) was  $160.5 \pm 13.3/93.8 \pm 8.7$  mmHg. After 4 months of therapy, OBP decreased by  $28.3 \pm 13.5/13.8 \pm 9.4$  to  $132.2 \pm 8.6/80.0 \pm 6.6$  mmHg ( $p < 0.0001$ ). Blood pressure targets were reached by 72.0 % of patients and by 81 and 91 % of patients previously treated with an angiotensin-converting enzyme inhibitor/hydrochlorothiazide or an angiotensin receptor blocker/hydrochlorothiazide, respectively. Changes in OBP were  $18.7 \pm 8.3/9.7 \pm 7.2$  mmHg for grade 1 ( $n = 1,679$ ),  $30.4 \pm 10.1/14.7 \pm 8.6$  mmHg for grade 2 ( $n = 2,397$ ), and  $45.4 \pm 15.1/20.7 \pm 12.1$  mmHg for grade 3 patients ( $n = 655$ ; all  $p < 0.0001$ ). In patients who underwent ambulatory blood pressure monitoring ( $n = 104$ ), 24-h mean blood pressure decreased from

$147.4 \pm 13.8/82.1 \pm 11.9$  to  $122.6 \pm 9.1/72.8 \pm 7.4$  mmHg ( $p < 0.0001$ ). Ankle edema was infrequent (0.2 % of patients).

**Conclusion** Triple combination perindopril/indapamide/amlodipine was effectively and safely administered to a large population of high- and very high-risk hypertensive patients who had not reached target OBP values with previous treatment.

## 1 Introduction

The morbidity and mortality challenges associated with long-term hypertension are such that controlling blood pressure has become a significant focus in global public health [1, 2]. Over the last 10 years, advancements in awareness and treatment strategies and changes in guidelines to include dual therapies have improved blood pressure control rates [3, 4]. However, a significant need to develop safer, more efficacious blood pressure control strategies still exists [5, 6].

As additional reductions in blood pressure and morbidity have been found with triple drug therapies compared with dual therapies and with single-pill formulations compared with free associations [7, 8], guidelines continue to support single-pill formulations and combinations that target multiple pathophysiological pathways and inhibit feedback loops [9]. The perindopril/indapamide/amlodipine combination is one possible triple-drug combination in which the calcium channel blocker (CCB) amlodipine and the diuretic indapamide mediate natriuresis and stimulate renin activity, while the angiotensin-converting enzyme (ACE) inhibitor perindopril inhibits the renin-angiotensin-aldosterone system (RAAS). Based on the current understanding of hypertension, the

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simultaneous targeting of these pathways would be expected to re-establish the balance between renin and sodium and, as a result, decrease blood pressure control and reduce adverse event rates generated by any one therapeutic class.

The combination of perindopril/indapamide/amlodipine is also supported by extensive blood pressure and clinical outcome data [10–19]. In particular, results from the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), HYVET (Hypertension in the Very Elderly), and ADVANCE (Action in Diabetes and Vascular Disease) trials suggest that, in addition to the blood pressure-lowering benefits, a perindopril/indapamide/amlodipine combination is likely to reduce mortality [12, 14, 18, 20, 21].

Consistent with these efficacy and tolerability expectations, data from the observational PIANIST trial, in which 12,064 patients with blood pressure that was not properly controlled were treated with a free combination of perindopril/indapamide/amlodipine, showed that after 4 months of treatment, significant changes from baseline in blood pressure were noted [22]. In the current study, we evaluated the efficacy and tolerability of single-pill perindopril/indapamide in free association with amlodipine in high- to very high-risk patients with essential hypertension that was not properly controlled despite previous treatment. The aim of this study was to evaluate this triple therapy in order to support the development of a safe and efficacious triple-drug fixed combination formulation and in order to offer an ACE inhibitor-containing alternative to currently marketed triple-drug therapy single pill combinations, all of which include an angiotensin receptor blocker (ARB).

## 2 Methods

### 2.1 Study Design

In this multicenter, prospective, observational, non-interventional, 4-month, open-label clinical study named PIANIST (Perindopril-Indapamide plus Amlodipine in high risk hyperTensive patients), patients at high or very high cardiovascular risk were enrolled if they had essential hypertension that was not properly controlled despite antihypertensive therapy. Patients were switched to treatment with fixed-dose combination perindopril 10 mg/indapamide 2.5 mg with the co-administration of amlodipine (2.5, 5.0, or 10 mg). As this was a non-interventional, observational trial, physicians (internists, hypertension specialists, cardiologists, or family practitioners) only enrolled patients for whom the switch to study drug was consistent with their existing therapeutic plan and in line with the summary of product characteristics of Coverex<sup>®</sup>-AS Komb Forte (international brand name is Preterax<sup>®</sup>) and Cardilopin<sup>®</sup>

(registration numbers: OGYI-T-20300 and OGYI-T-07604). Additional antihypertensive therapies were allowed. A subset of patients were, at the physician's discretion, enrolled in the ambulatory blood pressure monitoring (ABPM) substudy. This study was performed in accordance with the ethical standards described in the Declaration of Helsinki (1964; 1975; 1983) and was approved by the appropriate ethics committee (approval number by ETT-TUKEB-NIT: 31599/2011/EKU 936/PI/II).

### 2.2 Inclusion/Exclusion Criteria

Ambulatory patients who were over 18 years of age were enrolled if they had essential hypertension that was not properly controlled despite ongoing antihypertensive treatment and were at high or very high cardiovascular risk. Cardiovascular risk was defined as outlined in 2007 hypertension guidelines of the European Society of Cardiology/European Society of Hypertension [11].

In addition, women needed to be using an effective method of contraception or to have been postmenopausal for at least 1 year. All patients needed to have provided written informed consent. Patients were excluded if they had any contraindications to perindopril/indapamide or amlodipine, as set out in the summary of product characteristics (registration numbers: OGYI-T-20300 and OGYI-T-07604).

### 2.3 Measurements

Patients attended three visits (inclusion/baseline, month 1, and month 4). Patient history was collected during the baseline visit. Blood pressure and heart rate were collected at the physician's office at baseline, month 1, and month 4. Blood pressure was measured according to the 2009 Hungarian Society of Hypertension management guidelines [23]. Laboratory parameters (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, fasting glucose, hemoglobin A1c, serum creatinine, uric acid, microalbuminuria, estimated glomerular filtration rate [eGFR], potassium, and sodium) were determined at the discretion of the physician at baseline and month 4. Adverse events were recorded on case report forms at month 1 and month 4.

### 2.4 Statistics

Data were collected and analyzed according to European Guidelines for Good Clinical Practice/International Conference on Harmonisation (ICH) standards. As the aim of the study was to evaluate the efficacy of the triple-drug combination perindopril 10 mg/indapamide 2.5 mg/

amlodipine 5 or 10 mg, only patients taking these dosages of medication and for whom all blood pressure and heart rate data were available were included in the main cohort.

Data were analyzed using descriptive statistical methods. For quantitative variables, means and standard deviations are presented; for qualitative variables, *n* and percentages were calculated. Between-group comparisons were performed using one-sample *t* tests and Chi-squared tests. Significance for two-sided tests was set at 5 %.

Calculations were performed in the main cohort and in the subgroup of patients who had undergone ABPM. Data were analyzed according to grade of hypertension and pre-existing antihypertensive treatment (ACE inhibitor, ARB, ACE inhibitor + hydrochlorothiazide, ARB + hydrochlorothiazide, amlodipine, ACE inhibitor + amlodipine; ARB + amlodipine). Grade of hypertension was defined according to the 2007 hypertension guidelines of the European Society of Cardiology/European Society of Hypertension [11]: patients had grade 1 hypertension if their systolic blood pressure (SBP) was between 140 and 159 mmHg or their diastolic blood pressure (DBP) was between 90 and 99 mmHg; patients had grade 2 hypertension if their SBP was between 160 and 179 mmHg or their DBP was between 100 and 109 mmHg; patients had grade 3 hypertension if their SBP was  $\geq 180$  mmHg or their DBP was  $\geq 110$  mmHg.

Target office blood pressure was defined as SBP/DBP <140/90 mmHg. For ABPM, blood pressure control was defined as SBP/DBP <130/80 mmHg for 24-h blood pressure, <135/85 mmHg for daytime blood pressure, and <120/70 mmHg for nighttime blood pressure. Percent time elevation was defined as percentage of time over a 24-h period during which blood pressure was above 140/90 mmHg during the daytime and 120/80 mmHg during the nighttime. Blood pressure load was defined as percentage area under the blood pressure curve above previously defined values.

### 3 Results

The trial was conducted between 17 February 2012 and 18 September 2012, and was carried out at 762 centers in Hungary. Of the 10,163 patients enrolled in the PIANIST study, 5,432 were excluded from the analysis due to undocumented/other dose of amlodipine (*n* = 3,675), no evidence of high risk (*n* = 945), missing data for SBP/DBP/heart rate (*n* = 482), missing case report forms/misused visits (*n* = 181), and patient gender unknown or age unknown/less than 18 years (*n* = 149). Patients who met study and treatment dose criteria (perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 or 10 mg) were included in the analysis (*N* = 4,731).

Fifty percent of patients were female (Table 1). Mean age was  $63.8 \pm 11.1$  years and mean body mass index was  $29.9 \pm 5.3$  kg/m<sup>2</sup>. The proportion of patients with cardiovascular risk factors or target organ damage was high: dyslipidemia (63.9 %), family history of cardiovascular disease (51.4 %), obesity (45.4 %), smoking (36.7 %), ischemic heart disease (36.0 %), diabetes (32.9 %), peripheral artery disease (15.2 %), cerebrovascular disease (14.3 %), pre-diabetes (13.5 %), chronic heart failure (8.6 %), and chronic kidney disease (6.4 %). Patients were being treated with ACE inhibitors (63.1 %), beta-blockers (55.8 %), CCBs (44.4 %), diuretics (33.9 %), ARBs (12.8 %), or other antihypertensive medications (10.9 %), and more specifically with amlodipine (39.9 %), perindopril (23.3 %), hydrochlorothiazide (10.7 %), and indapamide (4.5 %).

Mean baseline office blood pressure was  $160.5 \pm 13.3/93.8 \pm 8.7$  mmHg and mean duration of hypertension was  $11.9 \pm 8.2$  years. Most patients had grade 2 hypertension (50.7 % of patients), followed by grade 1 hypertension (35.5 % of patients), and grade 3 hypertension (13.8 % of patients). Most patients were receiving two or more antihypertensive medications (75.1 %). Mean baseline office heart rate was  $79.3 \pm 9.2$  bpm.

In addition to perindopril 10 mg/indapamide 2.5 mg, 19.3 % of patients were prescribed 10 mg of amlodipine at baseline (vs. 80.7 % receiving 5 mg amlodipine); 28.4 % of patients were receiving 10 mg of amlodipine at month 1 (vs. 71.6 % receiving 5 mg amlodipine); and 29.0 % of patients were receiving 10 mg of amlodipine at month 4 (vs. 71.0 % receiving 5 mg amlodipine).

#### 3.1 Office Blood Pressure and Heart Rate

After 4 months of therapy, mean office blood pressure had decreased by  $28.3 \pm 13.5/13.8 \pm 9.4$  to  $132.2 \pm 8.6/80.0 \pm 6.6$  mmHg ( $p < 0.0001$ ; Fig. 1a), and mean heart rate had decreased by  $5.8 \pm 8.2$  to  $73.5 \pm 6.2$  bpm ( $p < 0.0001$ ). Significant decreases in blood pressure from baseline occurred regardless of the grade of baseline hypertension, with decreases in SBP/DBP of  $18.7 \pm 8.3/9.7 \pm 7.2$  mmHg for grade 1 patients,  $30.4 \pm 10.1/14.7 \pm 8.6$  mmHg for grade 2 patients, and  $45.4 \pm 15.1/20.7 \pm 12.1$  mmHg for grade 3 patients (all  $p < 0.0001$ ). Significant decreases from baseline in blood pressure also occurred regardless of previous antihypertensive treatment (Fig. 1b) with decreases in blood pressure of  $29.3 \pm 13.8/13.8 \pm 8.5$  mmHg in patients previously treated with ACE inhibitors,  $29.1 \pm 14.5/-15.2 \pm 10.9$  mmHg in patients previously treated with ARBs,  $28.2 \pm 13.2/13.6 \pm 9.6$  mmHg in patients previously treated with ACE inhibitor + hydrochlorothiazide,  $25.5 \pm 9.8/14.4 \pm 9.0$  mmHg in patients previously treated with ARB + hydrochlorothiazide,

**Table 1** Demographics and medical history at baseline ( $N = 4,731$ )

	<i>n</i>	%
Female	2,350	49.7
Age (y)		
<40	109	2.3
40–49	385	8.1
50–59	1,066	22.5
60–69	1,638	34.6
70–79	1,181	25.0
>80 years	352	7.4
Grade of hypertension <sup>a</sup>		
1	1,679	35.5
2	2,397	50.7
3	655	13.8
Cardiovascular risk factors		
Age (males >55 y, females >65 y)	3,046	64.4
Dyslipidemia	3,021	63.9
Obesity (BMI $\geq 30$ kg/m <sup>2</sup> )	2,150	45.4
Smoking	1,737	36.7
Positive family history	2,430	51.4
Pre-diabetes (FG 5.6–6.9 mmol/L)	639	13.5
Previous antihypertensive therapies		
ACE inhibitor	2,984	63.1
Beta-blocker	2,638	55.8
Calcium channel blocker	2,100	44.4
Diuretic	1,604	33.9
ARB	604	12.8
Other antihypertensive	518	10.9
Number of antihypertensive therapies		
0	390	8.2
1	787	16.6
2	1,464	30.9
3 or more	2,090	44.2
Co-morbidities		
Ischemic heart disease	1,705	36.0
Diabetes mellitus	1,555	32.9
Peripheral vascular disease	720	15.2
Transient ischemic attack/stroke	676	14.3
Chronic heart failure	409	8.6
Renal disease	302	6.4

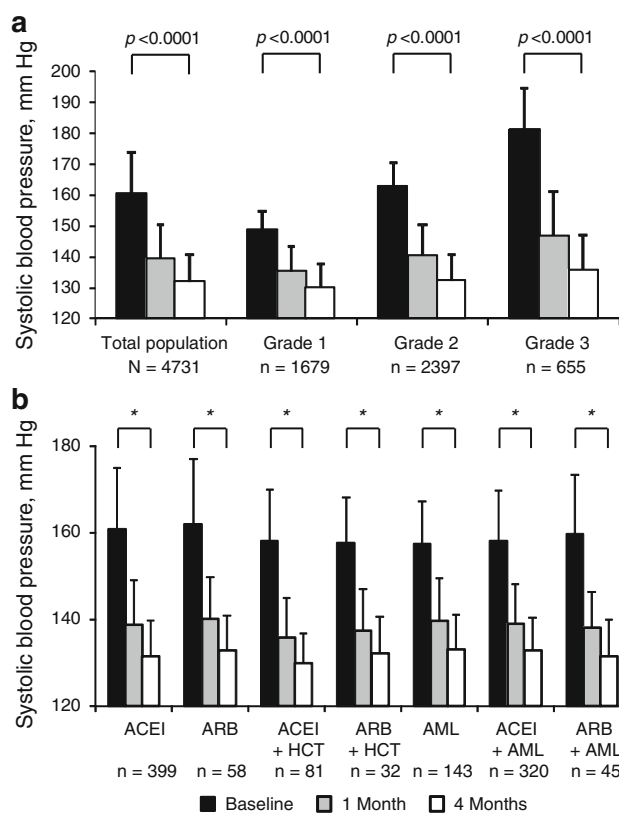
<sup>a</sup> Defined according to the European Society of Cardiology/European Society of Hypertension 2007 guidelines [11]

ACE angiotensin-converting enzyme, ARB angiotensin receptor blocker, BMI body mass index, FG fasting blood glucose

$24.1 \pm 10.8/11.6 \pm 8.0$  mmHg in patients previously treated with amlodipine,  $25.4 \pm 11.3/11.9 \pm 8.2$  mmHg in patients previously treated with amlodipine + ACE inhibitor, and  $28.2 \pm 13.7/14.5 \pm 8.5$  mmHg in patients previously treated with amlodipine + ARB (for all changes from baseline  $p < 0.0001$ ). Significant decreases from baseline in blood

pressure occurred regardless of the number of previous antihypertensive treatments, with decreases in blood pressure of  $31.7 \pm 15.2/15.1 \pm 10.2$  in previously untreated patients, of  $28.1 \pm 13.6/13.6 \pm 9.5$  in patients previously receiving monotherapy, of  $27.6 \pm 12.5/13.4 \pm 8.9$  in patients previously receiving dual therapy, and  $28.3 \pm 13.8/13.9 \pm 9.6$  in patients previously treated with three or more antihypertensives (for all changes from baseline  $p < 0.0001$ ). Significant decreases in heart rate were also noted regardless of previous antihypertensive treatment and number of previous antihypertensive treatments (data not shown).

Blood pressure targets were reached by 72.0 % of patients in the main cohort, 85.7 % of patients with grade 1 hypertension, 69.5 % of patients with grade 2 hypertension, and 46.3 % of patients with grade 3 hypertension. When data were analyzed in patients according to previous



**Fig. 1** Systolic blood pressure with triple-drug combination perindopril/indapamide/amlodipine. Patients were treated with triple-drug combination perindopril/indapamide/amlodipine for 4 months. **a** Systolic blood pressure decreased significantly over time regardless of baseline grade of hypertension. **b** Systolic blood pressure decreased significantly over time regardless of previous antihypertensive treatment. Means and standard deviations are presented. Statistical significance was set at  $p < 0.05$ . \* $p < 0.05$ . Grades of hypertension were defined according to the 2007 hypertension guidelines of the European Society of Cardiology/European Society of Hypertension [11]. ACEI angiotensin-converting enzyme inhibitor, AML amlodipine, ARB angiotensin receptor blocker, HCT hydrochlorothiazide

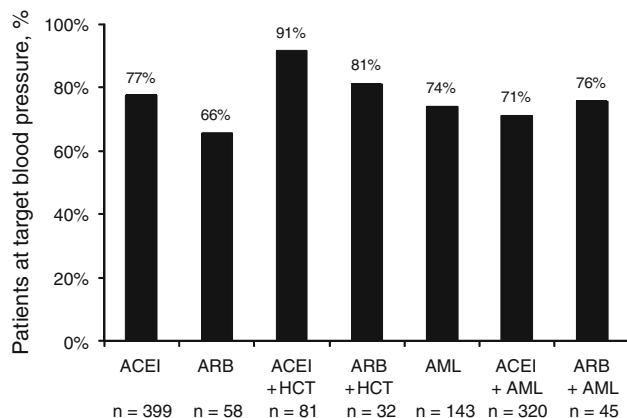
treatments (Fig. 2), 81 and 91 % of patients previously treated with an ACE inhibitor/hydrochlorothiazide or an ARB/hydrochlorothiazide reached blood pressure targets, respectively. When blood pressure targets were analyzed according to the number of previous antihypertensive treatments, blood pressure control was reached by 68.2 % of previously untreated patients, 73.8 % of patients previously receiving monotherapy, 73.3 % of patients previously receiving dual therapies, and 71.2 % of patients previously receiving three or more antihypertensive therapies.

### 3.2 Ambulatory Blood Pressure Monitoring

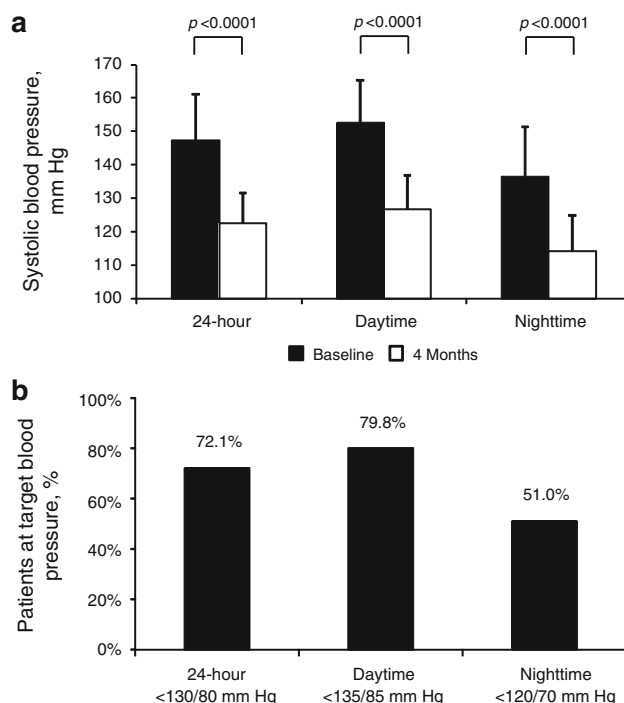
In the subgroup of 104 patients who underwent ABPM (Fig. 3), 24-h mean blood pressure decreased over 4 months of treatment from  $147.4 \pm 13.8/82.1 \pm 11.9$  to  $122.6 \pm 9.1/72.8 \pm 7.4$  mmHg ( $p < 0.0001$ ) and heart rate from  $73.2 \pm 9.9$  to  $71.1 \pm 8.5$  bpm ( $p = 0.03$ ). Twenty-four hour blood pressure targets were reached by 72.1 % of patients. Decreases in daytime and nighttime blood pressure and heart rate were also statistically significant: 79.8 and 51.0 % of patients reached blood pressure targets, respectively. Percent time elevation decreased significantly from  $69.5 \pm 24.9$  to  $21.7 \pm 18.7$  % for SBP (decrease of  $47.8 \pm 27.6$  %;  $p < 0.0001$ ) and from  $42.2 \pm 31.3$  to  $11.9 \pm 14.8$  % for DBP (decrease of

$30.4 \pm 29.6$  %;  $p < 0.0001$ ). Changes in blood pressure load were also significant as it decreased from  $340.6 \pm 289.5$  to  $56.0 \pm 63.0$  mmHg-h (decrease of  $284.6 \pm 280.4$  mmHg-h;  $p < 0.0001$ ) for SBP and  $125.9 \pm 168.8$  to  $19.7 \pm 27.3$  mmHg-h for DBP (decrease of  $106.2 \pm 159.6$  mmHg-h;  $p < 0.0001$ ).

When data were further analyzed by baseline grade of hypertension, 24-h mean blood pressure decreased by  $18.7 \pm 10.0/5.0 \pm 12.6$  mmHg in the grade 1 group from a baseline of  $141.2 \pm 6.0/77.7 \pm 12.7$  ( $n = 19$ ;  $p = 0.02$ ), by  $24.9 \pm 12.2/9.2 \pm 10.4$  mmHg in the grade 2 group from a baseline of  $146.4 \pm 11.3/81.6 \pm 10.5$  ( $n = 64$ ;  $p < 0.0001$ ), and by  $30.0 \pm 21.5/13.2 \pm 11.7$  mmHg in the grade 3 group from a baseline of  $155.9 \pm 20.7/87.6 \pm 13.8$  ( $n = 21$ ;  $p = 0.0003$ ). Heart rate decreased by a mean of  $3.6 \pm 6.9$  bpm from a baseline of  $74.1 \pm 8.6$  ( $p = 0.03$ ),  $2.7 \pm 11.0$  bpm from a baseline of  $73.5 \pm 10.1$  ( $p = 0.04$ ), and  $1.0 \pm 12.9$  bpm from a baseline of  $71.6 \pm 10.6$  ( $p = 0.7$ ) in the grade 1, 2, and 3



**Fig. 2** Office blood pressure targets after 4 months of treatment with triple-drug combination perindopril/indapamide/amlodipine. Patients were treated with triple-drug combination perindopril/indapamide/amlodipine for 4 months. Target blood pressure was reached by 66–91 % of patients depending on previous antihypertensive treatment. Target office blood pressure was defined as a systolic/diastolic blood pressure  $<140/90$  mmHg, except in patients with diabetes mellitus, metabolic syndrome, peripheral vascular disease, coronary heart disease, cerebrovascular disease and/or chronic renal failure for whom it was defined as a systolic/diastolic blood pressure of  $130\text{--}139/80\text{--}85$  mmHg. ACEI angiotensin-converting enzyme inhibitor, AML amlodipine, ARB angiotensin receptor blocker, HCT hydrochlorothiazide



**Fig. 3** Ambulatory blood pressure with triple-drug combination perindopril/indapamide/amlodipine. Patients were treated with triple-drug combination perindopril/indapamide/amlodipine for 4 months. Ambulatory blood pressure was measured at baseline and 4 months in 104 patients. **a** Changes in 24-h, daytime, and nighttime systolic blood pressure were statistically significant. Means and standard deviations are presented. Statistical significance was set at  $p < 0.05$ . **b** Daytime blood pressure control was reached by 79.8 % of patients. Nighttime blood pressure control was reached by 51.0 % of patients. Blood pressure control was defined as a systolic/diastolic blood pressure  $<130/80$  mmHg for 24-h blood pressure,  $<135/85$  mmHg for daytime blood pressure, and  $<120/70$  mmHg for nighttime blood pressure



groups, respectively. Twenty-four hour blood pressure targets were reached by 79.0, 75.0, and 57.1 % of patients in the grade 1, 2, and 3 groups, respectively.

### 3.3 Laboratory Parameters

Mean changes in sodium and potassium were not clinically significant (Table 2). Improvements in plasma levels of total cholesterol (−9.5 %), LDL cholesterol (−10.4 %), triglycerides (−11.5 %), fasting glucose (−4.9 %), hemoglobin A1c (−0.3 %), serum creatinine (−2.3 %), uric acid (−3.5 %), microalbuminuria (−28.0 %), HDL cholesterol (+3.7 %), and eGFR (+1.2 %) were noted.

### 3.4 Safety

Thirty-five patients reported a total of 38 adverse events, three of which were serious. The most frequently reported adverse events were ankle edema ( $n = 9$ ; 0.2 % of patients), hypotension ( $n = 6$ ; 0.1 % of patients), cough ( $n = 4$ ; 0.08 %), and dizziness ( $n = 4$ ; 0.08 %). The three serious adverse events that occurred (atrial fibrillation, stroke, and cerebral tumor) were considered unlikely to be related to study treatment.

## 4 Discussion

In this observational, every day practice, 4-month, open-label, clinical study of patients at high and very high cardiovascular risk, blood pressure control was significantly improved after 4 months of treatment with triple-drug

combination perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 or 10 mg. In these patients with difficult-to-treat hypertension who had been treated unsuccessfully with a wide range of antihypertensives, the switch to perindopril/indapamide/amlodipine led to a mean blood pressure decrease of 28.3/13.8 mmHg and an overall blood pressure control rate of 72 %. Adverse events, including edema, cough, and headache, were infrequent, and potassium levels were stable.

Despite the difficulties associated with treating high-risk patients, significant reductions in blood pressure were noted 1 month after the switch to perindopril/indapamide/amlodipine. Since 1-month response rates have been shown to be predictive of long-term cardiovascular events and survival [24], these data suggest that this triple-drug combination may have significant long-term benefits. In addition, significant reductions in blood pressure variability also suggest a likely long-term reduction in morbidity and mortality, as fluctuations in blood pressure over the course of a day have been shown to contribute significantly to end organ damage and cardiovascular risk [25].

Beyond the therapeutic class effects, the specific properties of perindopril, indapamide, and amlodipine suggest additional morbi-mortality benefits [15, 26, 27]. The combination of perindopril with indapamide has been shown to improve vascular endothelial function and target organ function and to decrease the risk of cerebrovascular and cardiovascular events [12, 13, 17–19, 28, 29]. The combination of perindopril with amlodipine has been shown to improve arterial stiffness and wave reflection, as well as cardiovascular outcomes such as stroke and coronary events [14, 30]. Lastly, unlike other ACE inhibitors or

**Table 2** Laboratory parameters after 4 months of treatment with triple-drug combination perindopril/indapamide/amlodipine

Parameter	<i>n</i>	Baseline, mean ± SD	4 months, mean ± SD	Difference	% change	<i>p</i>
TC, mmol/L	1,608	5.6 ± 1.1	5.0 ± 0.9	−0.5 ± 0.9	−9.5	<0.0001
HDL-C, mmol/L	993	1.4 ± 0.4	1.4 ± 0.4	0.0 ± 0.3	3.7	<0.0001
LDL-C, mmol/L	706	3.2 ± 1.0	2.8 ± 0.9	−0.3 ± 0.9	−10.4	<0.0001
TG, mmol/L	1,566	2.1 ± 1.0	1.8 ± 0.9	−0.2 ± 0.9	−11.5	<0.0001
Glucose <sup>a</sup> , mmol/L	1,615	6.3 ± 1.7	6.0 ± 1.4	−0.3 ± 1.1	−4.9	<0.0001
HbA <sub>1c</sub> , %	538	7.2 ± 4.2	7.2 ± 5.5	−0.0 ± 6.5	−0.3	<0.0001
Uric acid, μmol/L	1,276	323.0 ± 83.5	311.6 ± 77.8	−11.4 ± 61.6	−3.5	<0.0001
eGFR, mL/min/1.73 m <sup>2</sup>	734	61.2 ± 12.3	61.9 ± 12.6	0.8 ± 8.8	1.2	0.0002
Microalbuminuria, mg/24 h	252	46.5 ± 68.5	33.5 ± 52.4	−13.0 ± 31.3	−28.0	<0.0001
Creatinine, mmol/L	1,301	90.9 ± 25.0	88.8 ± 22.2	−2.1 ± 15.3	−2.3	<0.0001
Potassium, mmol/L	1,352	4.4 ± 0.5	4.4 ± 0.5	−0.0 ± 0.5	−0.5	0.004
Sodium, mmol/L	1,230	139.5 ± 8.4	139.4 ± 8.8	−0.2 ± 9.7	−0.1	0.4

Laboratory parameters were measured at the discretion of the physician at baseline and after 4 months of treatment

eGFR estimated glomerular filtration rate, HbA<sub>1c</sub> glycosylated hemoglobin A1c, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, SD standard deviation, TC total cholesterol, TG triglycerides

<sup>a</sup> Fasting

ARBs, perindopril plus indapamide sustained release (SR) in the HYVET trial, perindopril in fixed combination with indapamide in the ADVANCE trial, and perindopril in combination with amlodipine in the blood pressure-lowering arm of the ASCOT trial have shown additional and significant mortality benefits [20]. Long-term studies would be needed to confirm that the predicted improvements in organ protection and reduced mortality rates would extend to this triple-drug therapy.

The simultaneous targeting of the RAAS and natriuresis pathways was expected to lead to good tolerability. Indeed, the opposing effects of these three drugs are visible in the low adverse event rates. Edema rates (0.2 %) were low, reflecting opposing effects of perindopril and amlodipine on renin [31]; cough rates (0.08 %) were low, reflecting opposing effects of amlodipine on ACE inhibitor-induced coughs [32]; and no changes in potassium were observed, thereby reflecting the opposing effects of indapamide and perindopril [33, 34]. The low cough rate is also likely to be because perindopril has been shown to be associated with low rates of cough [35], and that 63 % of patients had previously been treated with an ACE inhibitor and would not have been susceptible to the cough associated with new treatment with an ACE inhibitor. The low overall adverse event rate in the study is also likely to reflect the well documented low adverse event profile of indapamide. Unlike thiazide diuretics, indapamide has been shown to be metabolically neutral and to have little effect on potassium levels and on lipid and glucose profiles [33, 34, 36].

Although guidelines state that ARBs can also be used as the RAAS inhibitor in triple drug combinations [9], meta-analyses suggest that ARBs perform less well than ACE inhibitors with regards to mortality [20, 37]. In a pooled analysis of 20 cardiovascular morbi-mortality trials ( $n = 158,998$ ), ACE inhibitors were associated with a 10 % reduction in all-cause mortality, whereas no significant reduction in mortality was found with ARB treatment [20]. These data thus suggest that, in patients who have no contraindications for ACE inhibitors, triple combinations with ACE inhibitors may represent a better long-term option than ARBs. Supporting this hypothesis, a recent subanalysis of the blood pressure arm of the ADVANCE trial showed that prescription of perindopril/indapamide in patients receiving a CCB at baseline reduced the relative risk of death by 28 % and of major cardiovascular events by 12 % [21].

#### 4.1 Study Limitations

This study was an uncontrolled, open-label study that lasted 4 months. The data presented herein should therefore be interpreted with the knowledge that a placebo effect could not be assessed.

The reductions in blood pressure in patients with grade 3 hypertension resulted in a mean blood pressure <140/90 mmHg. However, the control rate in this group was only 46.3 %. This putative discrepancy between these two sets of data reflects the fact that the standard deviations for this group were large and that these patients constitute the hardest to treat group.

The improvements in metabolic parameters that were observed in this study need to be interpreted with caution. Our study design does not allow us to differentiate between a direct effect of treatment on metabolic parameters and a secondary effect, because fewer antihypertensives with unfavorable metabolic effects were prescribed (data not shown).

## 5 Conclusions

The efficacy and safety results of this every day, clinical practice study support the development of perindopril/indapamide/amlodipine in a single-pill fixed-dose triple-drug formulation. Although this trial was not designed to evaluate long-term outcomes, extensive clinical data describing these drugs as monotherapies and dual therapies suggest that the impact of treatment with this triple combination on morbi-mortality rates would be significant.

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