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Abstract	*Introduction:* The blood pressure (BP) of most patients on antihypertensive monotherapy or bitherapy remains uncontrolled. Our study evaluated the efficacy of triple therapy with perindopril, amlodipine, and indapamide sustained release (SR) in patients with uncontrolled hypertension on previous antihypertensive therapy. *Methods:* This 4-month, multicenter, prospective, observational, open-label study included patients switched from previous antihypertensive therapy to triple therapy with perindopril, amlodipine, and indapamide SR. The main outcome was change in office BP from baseline to 4 months, as well as changes in 24-h ambulatory BP monitoring (ABPM) parameters in a subgroup of patients. *Results:*

	Age was 62.8 ± 11.3 years in 6,088 patients (55 % were male). Office BP at baseline was 158.1 ± 13.0/92.6 ± 8.8 mmHg. By 4 months, office BP decreased by 26.7 ± 13.3/12.9 ± 9.4 mmHg ($p < 0.001$). ABPM was performed in 62 patients. In these patients, 24-h systolic BP decreased (from 138.7 ± 12.5 to 125.5 ± 12.8 mmHg), as did 24-h diastolic BP (from 77.5 ± 11.4 to 70.4 ± 8.7 mmHg) (both $p < 0.0001$). Heart rate remained unchanged. In patients previously on renin-angiotensin-aldosterone system (RAAS) inhibitor/amlodipine, 24-h ambulatory systolic and diastolic BP decreased from 136.9 ± 12.8 to 125.4 ± 13.3 mmHg ($p = 0.0003$) and from 76.3 ± 12.6 to 70.2 ± 9.5 mmHg ($p = 0.0005$). In those previously on RAAS inhibitor/hydrochlorothiazide, 24-h ambulatory systolic and diastolic BP decreased from 137.8 ± 12.7 to 122.7 ± 15.4 mmHg ($p = 0.0039$) and from 73.6 ± 9.4 to 65.7 ± 7.3 mmHg ($p = 0.002$). Most (74 and 80 %, respectively) patients reached target ABPM values (<130/80 mmHg). *Conclusion:* A triple combination of perindopril, amlodipine, and indapamide SR controlled BP effectively in hypertensive patients uncontrolled by previous antihypertensive monotherapy or bitherapy, including RAAS inhibitor/amlodipine or RAAS inhibitor/hydrochlorothiazide combinations.
Footnote Information	on behalf of the PAINT Investigators.

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ORIGINAL RESEARCH ARTICLE

Triple Combination Therapy in Hypertension: The Antihypertensive Efficacy of Treatment with Perindopril, Amlodipine, and Indapamide SR

Dénes Páll · Ildikó Szántó · Zoltán Szabó

Abstract

Introduction The blood pressure (BP) of most patients on antihypertensive monotherapy or bitherapy remains uncontrolled. Our study evaluated the efficacy of triple therapy with perindopril, amlodipine, and indapamide sustained release (SR) in patients with uncontrolled hypertension on previous antihypertensive therapy.

Methods This 4-month, multicenter, prospective, observational, open-label study included patients switched from previous antihypertensive therapy to triple therapy with perindopril, amlodipine, and indapamide SR. The main outcome was change in office BP from baseline to 4 months, as well as changes in 24-h ambulatory BP monitoring (ABPM) parameters in a subgroup of patients.

Results Age was 62.8 ± 11.3 years in 6,088 patients (55 % were male). Office BP at baseline was 158.1 ± 13.0/92.6 ± 8.8 mmHg. By 4 months, office BP decreased by 26.7 ± 13.3/12.9 ± 9.4 mmHg ($p < 0.001$). ABPM was performed in 62 patients. In these patients, 24-h systolic BP decreased (from 138.7 ± 12.5 to 125.5 ± 12.8 mmHg), as did 24-h diastolic BP (from 77.5 ± 11.4 to 70.4 ± 8.7 mmHg) (both $p < 0.0001$). Heart rate remained unchanged. In patients previously on renin-angiotensin-aldosterone system (RAAS) inhibitor/amlodipine, 24-h ambulatory systolic and diastolic BP decreased from 136.9 ± 12.8 to 125.4 ± 13.3 mmHg ($p = 0.0003$) and from 76.3 ± 12.6 to 70.2 ± 9.5 mmHg ($p = 0.0005$). In those previously on RAAS inhibitor/hydrochlorothiazide, 24-h ambulatory systolic and diastolic BP decreased from 137.8 ± 12.7 to 122.7 ± 15.4 mmHg ($p = 0.0039$) and from 73.6 ± 9.4 to 65.7 ± 7.3 mmHg ($p = 0.002$). Most (74 and 80 %, respectively) patients reached target ABPM values (<130/80 mmHg).

Conclusion A triple combination of perindopril, amlodipine, and indapamide SR controlled BP effectively in hypertensive patients uncontrolled by previous antihypertensive monotherapy or bitherapy, including RAAS inhibitor/amlodipine or RAAS inhibitor/hydrochlorothiazide combinations.

1 Introduction

Hypertension is a severe public health problem with a prevalence of 35–40 % in the adult population [1]. Given the growing prevalence of excess weight and obesity, and aging of the hypertensive populations, a further increase in rate of hypertension is to be expected [2–4]. Hypertension enhances cardiovascular (CV) risk, which means that effectively reducing elevated blood pressure (BP) and reaching target BP values is expected to result in risk reduction. According to a recent meta-analysis, a decrease in systolic blood pressure (SBP) of 2 mmHg reduces the risks of stroke and coronary events by 10 and 7 %, respectively [5].

Several factors contribute to the development of essential hypertension, in particular increased circulating volume, sympathetic hyperactivity, increased total peripheral vascular resistance, and abnormal overactivity of the renin-angiotensin-aldosterone system (RAAS). In the majority of hypertensive patients, the cumulative effects of numerous factors contribute to high BP, making it hard to control: up to 70 % of hypertensive patients need combination therapy [6, 7], and earlier use of single-pill combinations in the

A1 on behalf of the PAINT Investigators.

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treatment of hypertension appears beneficial in terms of BP control and CV event reduction [8, 9]. Combining two antihypertensive agents from different classes has also been shown to be a more effective way of reducing BP than doubling the dose of a single agent [10]. Despite the advantages of dual- vs. monotherapy, dual-agent antihypertensive combinations still fail to control BP in over half (60 %) of hypertensive patients [7].

The 2007 Guidelines of the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) recommend five classes of antihypertensive as first-line treatment: diuretics, beta-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) [2]. As most hypertensive patients require combination therapy, this first-line approach needs reconsideration. The 2009 update of the ESH/ESC guidelines suggested slight modifications and shifts in emphasis, based on new studies [11]. The latest 2013 ESH/ESC guidelines have underlined the faster response to combination therapy in most patients, a better chance of achieving target BP in patients with higher BP, and improved patient adherence [12].

1.1 Aim

PAINT (Perindopril-Amlodipine plus Indapamide combination for controlled hypertension Non-intervention Trial) was principally designed to investigate the antihypertensive efficacy of a triple combination of antihypertensive drugs—perindopril, amlodipine, and indapamide sustained release (SR)—in patients who had not reached target BP values with previous antihypertensive treatment. As a secondary aim, changes in metabolic parameters were analyzed.

2 Patients and methods

Male or female Hungarian outpatients aged >18 years with primary hypertension took part in this prospective, multicenter, observational study. Grade 1 (mild) hypertension was classified as SBP 140–159 mmHg or diastolic blood pressure (DBP) 90–99 mmHg; grade 2 (moderate) hypertension as SBP 160–179 mmHg or DBP 100–109 mmHg; and grade 3 (severe) hypertension as SBP ≥180 mmHg or DBP ≥110 mmHg. Patients had uncontrolled BP on previous antihypertensive treatment [target of office <140/90 mm Hg; or <130/80 mmHg if ambulatory blood pressure monitoring (ABPM) data were available or if the patient had diabetes mellitus, metabolic syndrome, coronary heart disease, peripheral vascular disease, cerebrovascular disease, or chronic renal insufficiency] and were enrolled if their physician had planned to switch their antihypertensive therapy to fixed-dose combination perindopril/amlodipine 5/5, 5/10, 10/5, or 10/10 mg (Coveram®, Servier, Suresnes, France) plus indapamide SR 1.5 mg (Natrilix SR®, Servier). Patients with contraindications to any of these agents were excluded. Concomitant use of other RAAS inhibitors, CCBs, and/or diuretics was not permitted, but the concurrent use of other antihypertensive therapy, e.g., beta-blockers, alpha-adrenoreceptor blockers, and/or centrally acting antihypertensive drugs, was allowed. The decision on what dosage should be prescribed was made by physicians on the basis of recent BP values and existing comorbidities.

Because of the study's observational nature, office BP was measured in accordance with the usual method employed by the participating physician at baseline and 4 months. Patients from the main study who underwent ABPM as part of their follow-up were included as a subgroup in which ABPM and laboratory tests were performed at baseline and after 4 months using Meditech ABPM-04 or ABPM-05 devices (Meditech Ltd., Budapest, Hungary), validated by both the British Hypertension Society and the Association for the Advancement of Medical Instrumentation [13, 14]. Monitors were placed in the morning, and measurements were taken every 15 min during the day and every 30 min at night. From these measurements, 24-h daytime and night-time SBP and DBP, and heart rate were calculated. Percent time elevation was the percentage of the whole monitoring period when BP exceeded normal values (>140/90 mmHg during daytime and >120/80 mmHg during nighttime). Trough-to-peak (T/P) ratio was measured to characterize the quality of BP reduction. Laboratory parameters were determined at the discretion of the physician at baseline and after 4 months and included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, serum creatinine, uric acid, potassium, and sodium. Adverse events were recorded on specific case report forms over the 4 months of the study.

All patients provided written informed consent. This study was performed in accordance with the ethical standards described in the Declaration of Helsinki and was approved by the appropriate ethics committee (ETT-TU-KEB-NIT approval number: 4975-0/2010-1018EKU 333/PI/10).

2.1 Statistical methods

Baseline characteristics are summarized as means ± standard deviations for continuous variables, and numbers of patients and percentages for categorical variables, and analyses were performed on an intention-to-treat basis. Mean changes in office BP are shown according to severity of hypertension and previous monotherapy or RAAS

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inhibitor bitherapy, as well as according to perindopril/amlodipine dosage during the study (5/5, 5/10, 10/5, or 10/10 mg). In the ABPM subgroup, changes in mean SBP and DBP are shown according to severity of hypertension at baseline, as well as before and after treatment. A paired *t* test was used to assess whether changes in office- or ABPM-assessed SBP and DBP from baseline to 4 months were significant. Significance was defined as *p* value <0.05. Data were collected and analyzed in accordance with the European Guidelines for Good Clinical Practice/ICH guidelines. Planimeter Kft. (Budapest, Hungary), an independent statistics company, analyzed all study data using SAS software (version 9.3).

3 Results

3.1 Baseline Characteristics

Mean age of the 6,088 patients in our study was 62.8 ± 11.3 years, and they had had hypertension for 11.2 ± 8.2 years. Most patients (90 %) had mild ($n = 2,424$) or moderate ($n = 3,033$) hypertension on previous antihypertensive treatment; some ($n = 631$) had severe hypertension. Over a third of patients had previously received three or more antihypertensive agents [$n = 2,164$ (36 %)] and over a third had received two antihypertensive agents [$n = 2,240$ (37 %)]; 28 % ($n = 1,684$) had received one antihypertensive agent. Other demographic and baseline data are presented in Table 1.

3.2 Office Blood Pressure

Mean office SBP decreased significantly from 158.1 ± 13.0 to 131.4 ± 8.4 mmHg from baseline to 4 months with perindopril/amlodipine/indapamide SR, and mean DBP decreased significantly from 92.6 ± 8.8 to 79.7 ± 6.2 mmHg (BP change, 26.7 ± 13.3/12.9 ± 9.4 mmHg; $p < 0.001$). The reductions in both office SBP and DBP were baseline dependent (Fig. 1); in cases where hypertension was more severe, the decrease in BP was greater. BP decreased significantly in all patients who previously took RAAS inhibitors or amlodipine monotherapy or ACE inhibitor- or ARB-based single-pill combinations (all $p < 0.0001$) (Fig. 2). The percentages of patients who achieved office BP control at the end of the study were 75, 76, and 78 % in patients previously receiving three or more, two, or one antihypertensive agent(s), respectively.

BP was also found to decrease significantly in each of the four dosage-based subgroups of perindopril/amlodipine/indapamide SR (all $p < 0.0001$) (Fig. 3). Office BP target was achieved after 4 months' treatment with

Table 1 Baseline characteristics in the 6,088 patients. Values are mean ± standard deviation or numbers and percentages

Parameter	Whole population ($n = 6,088$)
Demographic parameters	
Age (years)	62.8 ± 11.3
Male	3,353 (55 %)
Waist circumference (cm)	99.4 ± 13.3
Blood pressure parameters	
Systolic blood pressure (mmHg)	158.1 ± 13.0
Diastolic blood pressure (mmHg)	92.6 ± 8.8
Duration of hypertension (years)	11.2 ± 8.2
Risk factors	
Dyslipidemia	3,209 (53 %)
Obesity	3,157 (52 %)
Smoking	1,836 (30 %)
Prediabetes	773 (13 %)
Comorbidities	
Diabetes mellitus	1,605 (26 %)
Ischemic heart disease	1764 (29 %)
Transient ischemic attack/stroke	721 (12 %)
Renal disease	253 (4 %)
Peripheral vascular disease	613 (10 %)
Chronic heart failure	412 (7 %)

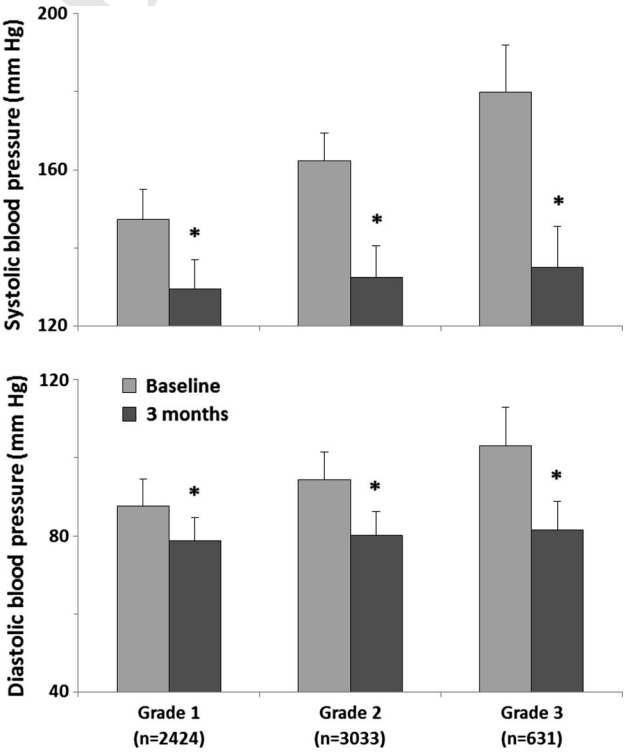

Fig. 1 Changes in office blood pressure from baseline to 4 months, according to severity of hypertension. Values are means ± standard deviations. *$p < 0.001$ vs. baseline. Mild hypertension (grade 1), systolic blood pressure (SBP) 140–159 mmHg, and/or diastolic blood pressure (DBP) 90–99 mmHg; moderate 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

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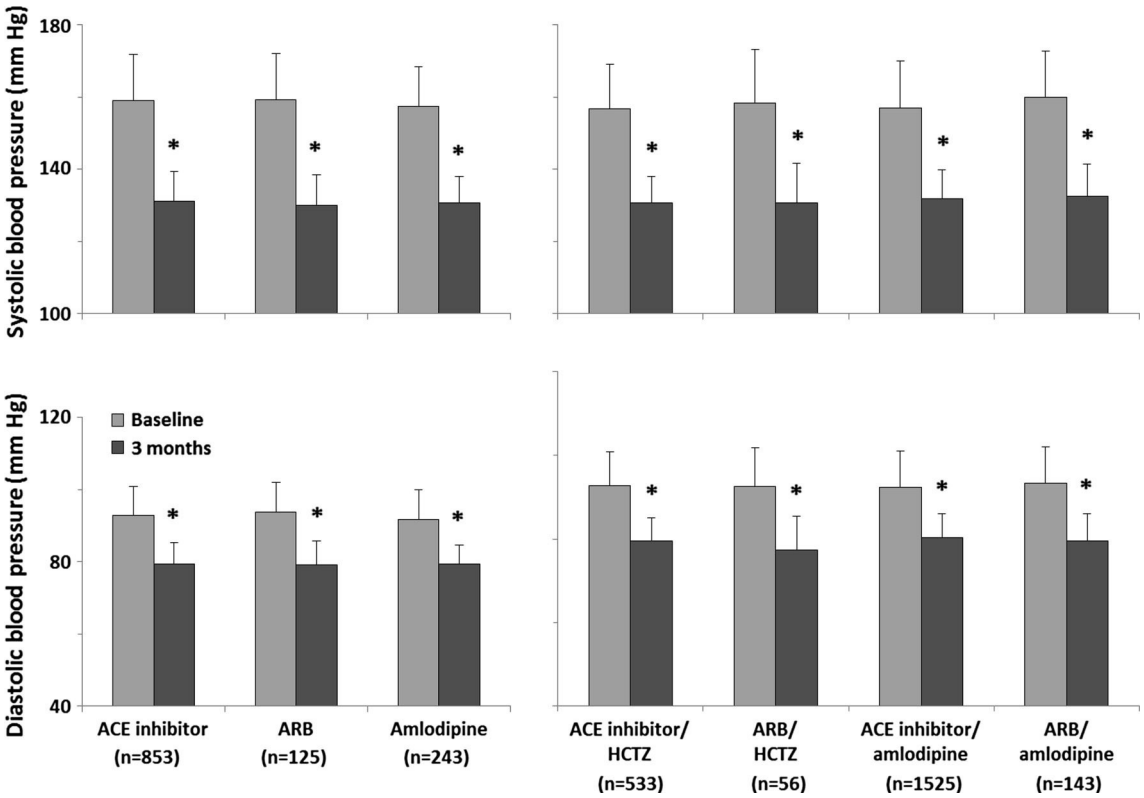

Fig. 2 Changes in office blood pressure from baseline to 4 months in patients previously on angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or amlodipine monotherapy (*left-hand panels*) or on ACE inhibitor- or ARB-based single-pill combinations (*right-hand panels*). Values are means ± standard deviations. HCTZ, hydrochlorothiazide. *$p < 0.0001$ vs. baseline

perindopril/amlodipine/indapamide SR by ≥70 %, regardless of dosage. The target was achieved by 80, 77, 73, and 71 % of patients on perindopril/amlodipine 5/5, 5/10, 10/5, and 10/10 mg plus indapamide SR 1.5 mg, respectively. Over the course of the study, the percentage of patients on perindopril/amlodipine 5/5 mg plus indapamide SR 1.5 mg decreased from 46 to 36 % (2,805–2,203 patients), while the percentage on perindopril/amlodipine 10/10 mg plus indapamide SR 1.5 mg increased from 25 to 33 % (1,500–1,994 patients). Smaller changes were observed in the use of perindopril/amlodipine 5/10 mg plus indapamide SR 1.5 mg (7 vs. 7 %; 399 vs. 397 patients) and perindopril/amlodipine 10/5 mg plus indapamide SR 1.5 mg (23 vs. 25 %; 1,384 vs. 1,494 patients).

3.3 ABPM Results

In total, 62 patients underwent ABPM. Thirty-four patients were previously on three or more antihypertensive agents, 14 were on antihypertensive bitherapy, and 14 were on antihypertensive monotherapy. At baseline, mean 24-h BP was 138.7 ± 12.5/77.5 ± 11.4 mmHg. Switching to perindopril/amlodipine/indapamide SR for 4 months significantly reduced both mean 24-h SBP and DBP to 125.5 ± 12.8/70.4 ± 8.7 mm Hg (−13.2 ± 13.7 and −7.1 ± 9.0 mmHg, respectively; both $p < 0.0001$), and normalized office BP in >80 % ($n = 50$) of patients. The reductions in mean 24-h BP were 10.2 ± 13.8/6.0 ± 8.7 mmHg in grade 1 patients ($n = 20$), 13.2 ± 13.9/7.8 ± 9.3 mmHg in grade 2 patients ($n = 33$), and 19.6 ± 12.0/7.2 ± 9.7 mmHg in grade 3 patients ($n = 9$) (all $p < 0.0001$) (Fig. 4). Overall, heart rate remained unchanged with this therapy (71.6 ± 8.9 vs. 70.0 ± 8.8 bpm; $p =$ not significant).

Analyzing daytime BP revealed significant reductions in both systolic and diastolic values [142.6 ± 13.7 at baseline vs. 129.2 ± 13.7 mmHg at 4 months for SBP; and 80.9 ± 13.0 at baseline vs. 73.6 ± 9.7 mmHg at 4 months for DBP (both $p < 0.0001$)]. Similar reductions in night-time BP were observed: SBP fell from a baseline value of 130.8 ± 14.3 to 118.0 ± 13.6 mmHg, while DBP fell from 70.8 ± 9.7 to 64.2 ± 8.4 mmHg ($p < 0.0001$).

Reduction in percent time elevation was significant for both SBP (72.5 ± 24.8 vs. 45.2 ± 31.6 %; $p < 0.0001$) and DBP (43.0 ± 34.2 vs. 21.8 ± 23.9 %; $p < 0.0001$). The diurnal index, which represents differences in daytime and night-time BP, increased slightly during the study before normalizing at the end of the observation period

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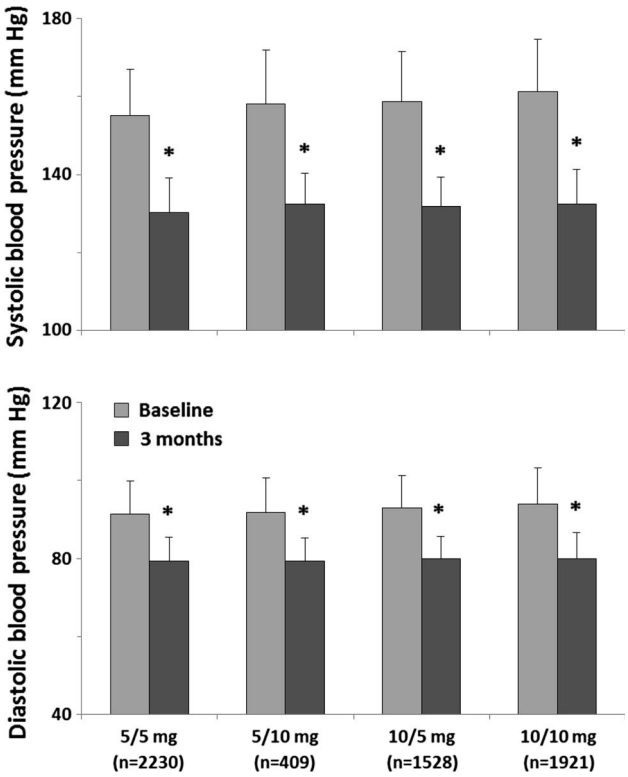

Fig. 3 Changes in office systolic and diastolic blood pressure from baseline to 4 months, according to dosage of perindopril/amlodipine during the study. Values are means ± standard deviations in patients receiving indapamide sustained release 1.5 mg. *$p < 0.0001$ vs. baseline

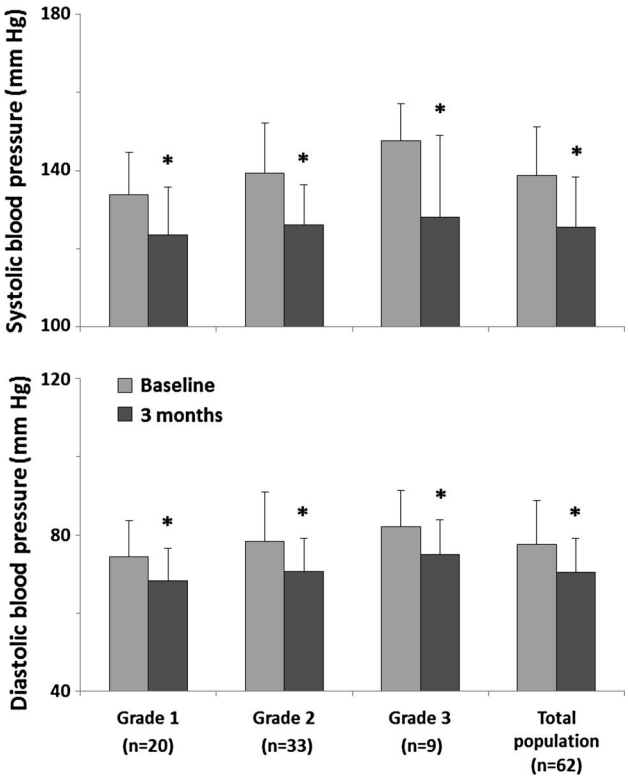

Fig. 4 The effect of perindopril/amlodipine/indapamide sustained release on systolic and diastolic blood pressure according to severity of hypertension, as measured by ambulatory blood pressure monitoring from baseline to 4 months ($n = 62$). Values are means ± standard deviations. *$p < 0.0001$ vs. baseline

[systolic value: 7.9 ± 9.1 vs. 8.5 ± 7.5 %; diastolic value: 11.7 ± 9.2 vs. 12.3 ± 8.5 % (both p = not significant)].

In patients on single-pill RAAS inhibitor/amlodipine ($n = 18$) switched to triple therapy, 24-h SBP decreased from 136.9 ± 12.8 at baseline to 125.4 ± 13.3 mmHg at 4 months ($p = 0.0003$), and 24-h DBP from 76.3 ± 12.6 to 70.2 ± 9.5 mmHg ($p = 0.0005$). There was no change in heart rate (70.6 ± 8.1 to 69.2 ± 9.7 bpm; $p = 0.54$). In patients on single-pill RAAS inhibitor/hydrochlorothiazide (HCTZ) switched to triple therapy ($n = 10$), 24-h SBP decreased from 137.8 ± 12.7 at baseline to 122.7 ± 15.4 mmHg at 4 months ($p = 0.0039$), and 24-h DBP from 73.6 ± 9.4 to 65.7 ± 7.3 mmHg ($p = 0.002$). Again, there was no change in heart rate (70.8 ± 10.7 to 71.9 ± 11.3 bpm; $p = 0.43$). Target 24-h ABPM values (<130/80 mmHg) were attained in 74 and 80 % of patients switched from single-pill RAAS inhibitor/amlodipine or RAAS inhibitor/HCTZ, respectively.

Reductions in BP were significant at each hour and in each hypertensive-class subgroup (10.1–15.4/5.1–7.8 mmHg; $p < 0.001$; Fig. 5). The T/P ratio with perindopril/amlodipine/indapamide SR was 75 % for SBP and 70 % for DBP.

3.4 Changes in Metabolic Parameters

Positive changes in metabolic parameters were also observed in the total study population. Total cholesterol decreased from 5.8 ± 1.1 to 5.2 ± 0.9 mmol/L, low-density–lipoprotein cholesterol from 3.3 ± 1.1 to 2.9 ± 0.9 mmol/L, triglycerides from 2.1 ± 1.1 to 1.9 ± 1.5 mmol/L, and blood glucose levels from 6.3 ± 1.7 to 5.9 ± 1.4 mmol/L (all $p < 0.0001$). High-density–lipoprotein cholesterol increased from 1.3 ± 0.4 mmol/L to 1.4 ± 0.4 mmol/L ($p = 0.0003$).

3.5 Safety

In the overall population ($n = 6088$), there were no serious adverse events. Patients experienced 43 adverse events during the study that were deemed drug related (0.7 %). The most common of these was ankle edema ($n = 34$; 0.6 %), but dizziness ($n = 3$; <0.1 %), headache ($n = 3$; <0.1 %), cough ($n = 2$; <0.1 %), and flushing ($n = 1$; <0.1 %) were also observed.

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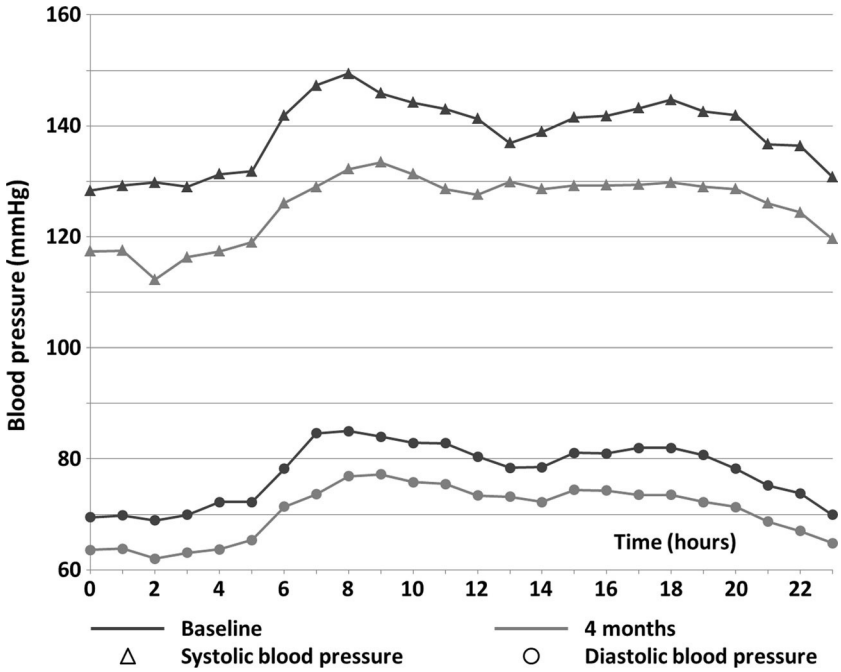

Fig. 5 Changes in mean systolic and diastolic blood pressure before (*baseline*, *dark gray lines*) and after (4 months, *light gray lines*) switch to triple therapy with perindopril/amlodipine/indapamide sustained release in the ambulatory blood pressure monitoring subgroup ($n = 62$)

4 Discussion

Switching hypertensive patients with uncontrolled BP on previous antihypertensive treatment to one of four dosages of a triple combination of perindopril/amlodipine/indapamide SR resulted in significant reductions in office and 24-h BP after 4 months, regardless of the dosage of triple therapy used or severity of hypertension at baseline. Office BP targets were achieved by most patients after 4 months' treatment. Metabolic parameters improved over the course of the study, adverse effects observed were those expected, and the incidence of adverse effects in the overall population was low. Our study confirms a previous finding that triple antihypertensive combination therapy with a RAAS inhibitor, CCB, and diuretic reduces BP more than component dual-combination treatment [10]. It also confirms recent findings showing that antihypertensive triple therapy in general [15, 16], and this triple combination in particular [17], reduce BP in hypertension.

Recent recommendations have emphasized the importance of inhibiting excess RAAS activity in the treatment of primary hypertension [2, 11]. Inhibition of an overactive RAAS can be achieved either with ACE inhibitors or ARBs, although recent meta-analyses have shown that ACE inhibitors may be better at reducing risk of CV and all-cause mortality [18, 19]. CCBs and diuretics can be added to ACE inhibitors to obtain an additional antihypertensive effect. The CCB with the most evidence for beneficial effects is the third-generation dihydropyridine amlodipine. With respect to diuretics, current evidence favors indapamide over HCTZ [20]. These combinations are recommended for priority use by current European hypertension guidelines [12]. Recent results from a post hoc analysis of ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN MR Controlled Evaluation) patients with type 2 diabetes mellitus showed that the addition of CCB to treatment with single-pill perindopril/indapamide significantly reduced the relative risk of all-cause mortality by 28 % compared with patients receiving standard therapy that included a CCB [21].

T/P ratio is an important indicator of duration of effect [22] and the SBP (75 %) and DBP (70 %) T/P ratios with triple therapy were above 66 %, the T/P threshold for safe single-daily-dose administration. This confirms the rationale for daily dosing with triple therapy. The circadian BP dipping profile was normalized by treatment, as seen by changes in systolic and diastolic diurnal index (>10 %). Antihypertensive regimens that include single-pill combinations are simpler, and improvements in patient compliance have been shown to lead to better BP reduction and control [10].

Throughout the 4-month observation period, significant beneficial changes were found in metabolic parameters: both blood glucose and lipid levels were reduced significantly. This might be due to the switching of many patients on HCTZ to the metabolically neutral agent, indapamide SR, used in this study [23], and also to the close follow-up of participants, which might have encouraged better compliance. The improvement in metabolic parameters seen with the combination of the three antihypertensive agents used in this study is in line with previous observations [17].

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Antihypertensive triple combinations also have the potential to reduce the severity and incidence of adverse effects. The severity of adverse effects may be minimized by combining antihypertensive agents with complementary modes of action [24]. ACE inhibitors in combination with CCBs have been shown to reduce the incidence of CCB-associated edema and diuretic-associated hypokalemia [24, 25]. The low incidence of adverse effects observed in this study may be attributable to these specific ACE inhibitor- and dihydropyridine CCB-related mechanisms of action, plus the metabolic neutrality of indapamide SR [26].

4.1 Limitations

Single-arm, open-label studies such as ours do not use randomized protocols. However, our findings do give an indication of the value of perindopril/amlodipine/indapamide SR in real-life clinical practice. Although only short-term benefit was evaluated here, the efficacy and safety of all three agents have been determined in international randomized controlled trials of several years' duration [27–29]. It can also be difficult to determine if a drug in a combination is ineffective [12]. However, the advantages of initiating antihypertensive therapy with a combination in patients with markedly elevated BP or at high/very high CV risk outweigh this constraint. The use of additional antihypertensive agents, which could have impacted our results, was not noted. The geographical scope of recruitment was limited to one country, but these data give a good picture of CV risk in hypertensive patients at a national level, which is of interest [30].

5 Conclusion

The triple combination of amlodipine, perindopril, and indapamide SR controlled BP effectively in hypertensive patients not controlled on previous antihypertensive monotherapy or bitherapy, including RAAS inhibitor/amlodipine or RAAS inhibitor/HCTZ combinations.

Conflict of interest The authors have no conflicts of interest that are directly relevant to the content of this article.

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