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Optimization of Blood Pressure Treatment with Fixed-Combination Perindopril/Amlodipine in Patients with Arterial Hypertension

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Abstract

Background: Fixed-dose combination treatments using an angiotensin-converting enzyme (ACE) inhibitor, such as perindopril, plus a calcium channel blocker (CCB), such as amlodipine, have been endorsed by guidelines because they improve blood pressure control and cardiovascular outcomes in hypertensive patients, while being well tolerated and well adhered to by patients.

Objective: This study aimed to assess the blood pressure-lowering effects of fixed-combination perindopril/amlodipine in patients previously treated with an ACE inhibitor and/or a CCB.

Methods: This was a prospective, real-life, open-label, longitudinal, phase IV study conducted in 223 outpatient medical centres across Slovakia. 2132 previously treated patients whose hypertension was insufficiently controlled at baseline or who tolerated treatment poorly were included. Patients were treated for 3 months with fixed-combination perindopril/amlodipine 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg. The main outcome measure was a reduction in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) and achievement of blood pressure targets (SBP/DBP <140/90 mmHg or <130/80 mmHg for patients with type 2 diabetes mellitus or high cardiovascular risk).

Results: After 3 months of treatment, mean ± SD SBP/DBP had decreased from 158.5 ± 17.5/93.6 ± 9.8 mmHg to 132.9 ± 10.6/80.7 ± 6.2 mmHg ($p < 0.0001$). In patients with grade 3 hypertension, mean ± SD changes from baseline in SBP/DBP were −45.4 ± 16.4/−20.0 ± 11.5 mmHg after 3 months ($p < 0.0001$). Blood pressure targets were reached by 74% of the overall patient population, 84% of patients with grade 1 hypertension, and 52% of difficult-to-treat patients with grade 3 hypertension. This treatment was associated with a 58% reduction in the number of patients with amlodipine-related ankle oedema compared with baseline.

Conclusion: Fixed-combination perindopril/amlodipine was well tolerated and resulted in statistically significant and clinically meaningful decreases in blood pressure.

Introduction

Although the understanding and awareness of the role of hypertension in cardiovascular disease continues to increase, the World Health Organization still describes hypertension as the number one risk factor for mortality with 13% of worldwide deaths being attributable to hypertension-related diseases.[1] Indeed, patients with uncontrolled hypertension are routinely encountered in daily medical practice and constitute an ongoing challenge for many physicians.

It is now well recognized that many patients require two or more antihypertensive medications to reach and maintain blood pressure control.[2] As a result, combination therapies have been strongly endorsed by guidelines as first-line and second-line therapeutic alternatives. Recently, guidelines have specified that strategies that combine renin-angiotensin-aldosterone system (RAAS) inhibitors with a calcium channel blocker (CCB) or a diuretic should be favoured in order to maximize the possible synergies between molecular pathways and mechanisms of action.[3] In particular, combining an angiotensin-converting enzyme (ACE) inhibitor, such as perindopril, with a dihydropyridine CCB, such as amlodipine, is expected to offer improvements in blood pressure and cardiovascular outcomes, while increasing venous outflow and reducing oedema associated with amlodipine treatment.[4,5] Furthermore, guidelines have endorsed single-pill formulations as they are believed to increase treatment adherence and reduce medication errors.[3]

Treatment of hypertension with perindopril/amlodipine, recently approved as a fixed-dose combination (FDC), meets guideline recommendations and is supported by the results of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) as well as by extensive data describing each drug as a monotherapy.[3-6] In the ASCOT trial, treatment of hypertensive patients with a combination of a CCB (amlodipine) and an ACE inhibitor (perindopril) clearly reduced mortality and cardiovascular events compared with treatment with a β-adrenoceptor antagonist/thiazide diuretic strategy.[7] Furthermore, amlodipine, which is also used for angina reduction in patients with coronary artery disease, has been shown to reduce blood pressure and cardiovascular events in patients with hypertension and/or coronary artery disease.[8-11] Perindopril has been shown to effectively reduce blood pressure, to improve endothelial function and hypertension-related abnormalities of arterial structure and function, to delay atherosclerosis, and to significantly reduce cardiovascular outcomes and mortality in a wide range of patients.[12-16] Together these data underscore the benefits of combining perindopril and amlodipine.

The objective of our study, named SYMBIO (StudY of optiMized Blood pressure lowering therapy with fixed cOmbination perindopril/amlodipine), was to assess, under real-life clinical practice conditions, the blood pressure-lowering effects and tolerability of perindopril/amlodipine FDC in patients who were being treated with an ACE inhibitor and/or a CCB, but had uncontrolled hypertension, and in controlled patients who poorly tolerated treatment with their previous ACE inhibitor and/or CCB.

Patients and Methods

In this prospective, open-label, longitudinal, phase IV study, cardiologists, internists, and general practitioners in Slovakia were instructed to consider for enrollment patients who were being treated for hypertension with an ACE inhibitor and/or a CCB (preferably amlodipine) and for whom the decision to prescribe perindopril/amlodipine FDC had already been made by the treating physician. Patients needed to either have arterial hypertension that was insufficiently controlled (systolic blood pressure [SBP]/diastolic blood pressure [DBP]

≥140/90 mmHg or ≥130/80 mmHg for patients with type 2 diabetes mellitus or high cardiovascular risk[2]) or controlled blood pressure under treatment but experiencing symptoms suggestive of poor treatment tolerability to the ACE inhibitor and/or CCB. Patients were excluded if: they were under the age of 18 years; had a known hypersensitivity or intolerance to perindopril or amlodipine; had had acute myocardial infarction or acute stroke within the previous 3 months; had diagnosed or suspected secondary hypertension; had a serious illness affecting their prognosis; or had a contraindication to treatment (such as pregnancy or breastfeeding).

The SYMBIO study conformed to the Declaration of Helsinki ethical principles for medical research involving human subjects. The protocol was approved by the Ethics Committee of the National Cardiovascular Institute in Bratislava, Slovakia. All patients were informed about the study by the participating physicians and patients provided their consent.

At baseline (month 0) existing treatments with an ACE inhibitor, CCB or an ACE inhibitor/CCB combination were replaced by perindopril/amlodipine 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, or 10 mg/10 mg FDC (Prestance®, Servier [Ireland] Industries Ltd, Wicklow County, Ireland) in the dosages chosen by the treating physician based on diagnosis and previous antihypertensive therapy. Other background treatments remained unchanged till the end of the study. Concomitant antihypertensive medications were allowed. In order to mirror real clinical practice conditions and to avoid a transient increase in blood pressure, no washout period was planned before changing antihypertensive medications. Study visits took place after 1 month and 3 months of treatment. At these visits, the physician was allowed to adjust the dosage of perindopril/amlodipine FDC based on efficacy and tolerability. No dose up-titration of concomitant antihypertensive medications was allowed.

Clinical Evaluations

Family history, concomitant diseases, cardiovascular risk factors, ankle oedema caused by therapy, and efficacy and tolerability of previous treatments for hypertension were recorded at baseline. Associated stable coronary artery disease and angina had to be confirmed by angiography, a history of myocardial infarction, and/or medical/hospital records. Presence of subclinical organ damage (such as left ventricular hypertrophy) had to be confirmed by a previous electrocardiogram or echocardiography.

Blood pressure and heart rate were evaluated at each visit. Blood pressure was measured in the sitting position, after 10 minutes of resting, using a manual sphygmomanometer according to the guidelines.[2] At least two measurements were made at every visit. Hypertension severity and target blood pressure values were defined according to the 2007 ESC/ESH hypertension guidelines with normal/high normal blood pressure values being defined as a SBP <140 mmHg and/or a DBP <90 mmHg; grade 1 hypertension as a SBP between 140 and 159 mmHg and/or a DBP between 90 and 99 mmHg; grade 2 hypertension as a SBP between 160 and 179 mmHg and/or a DBP between 100 and 109 mmHg; grade 3 hypertension as a SBP ≥180 mmHg and/or a DBP ≥110 mmHg.[2] Target values were defined as a SBP/DBP <140/90 mmHg or <130/80 mmHg for patients with type 2 diabetes or with high cardiovascular risk. Heart rate was measured after 10 minutes of resting from the radial pulse.

Safety and tolerability were assessed at each visit by recording subjective complaints and specifically evaluating ankle oedema. Physicians were asked to distinguish between ankle oedema due to worsening heart failure and oedema due to chronic venous disease. Any serious adverse events were reported in accordance with the SIDC No. 15/2004 instructions for registered drugs (the guidelines for reporting adverse drug reactions of registered medicinal products in the Slovak republic).

Statistical Analysis

The main outcome measures were the proportion of patients who achieved control and the mean change in blood pressure from baseline. Main descriptive statistics were performed on the intent-to-treat population. Subgroup analyses according to the baseline treatment were performed

using the final cohort of patients (patients having undergone 3 months of treatment with perindopril/amlodipine).

Means and standard deviations were calculated for linear variables; absolute numbers and percentages were calculated for categorical variables. For linear variables, when possible, Student's t-tests and analysis of variance (ANOVA) were used to evaluate between-group differences. For categorical variables, chi-squared (χ^2) tests and Fisher's exact tests were used to evaluate the differences between groups. Paired Student's t-tests were used to analyse changes from baseline. The hypothesis was considered statistically significant if $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences version 8.0 (SPSS Inc., an IBM company, Chicago, IL, USA).

Results

Between February and May 2009, 2132 patients were included in the intent-to-treat population and received 3 months of treatment with perindopril/amlodipine in 223 centres across Slovakia. Baseline patient and treatment characteristics are detailed in table I. The majority of patients had grade 1 (33%) or grade 2 (43%) hypertension. Seven percent of patients with controlled hypertension (n = 140) were included. Reasons for inclusion were poor treatment adherence (n = 123) and poor treatment tolerability (n = 17). Seventy-seven percent of patients had been taking ACE inhibitors (perindopril [32%], trandolapril [15%], ramipril [12%], lisinopril [8%], quinapril [6%], and others [3%]) and 59% had been taking a CCB (amlodipine for 86% of them). 230 patients were taking neither ACE inhibitors nor CCBs at baseline.

Sixty-six patients (3%) did not complete the study. The main reasons reported for discontinuation were loss to follow-up (n = 65) and asthenia (n = 1); the final cohort included 2066 patients.

Decreases in Blood Pressure and Blood Pressure Normalization after Treatment

At baseline, perindopril/amlodipine 5 mg/5 mg, 10 mg/5 mg, 10 mg/10 mg and 5 mg/10 mg FDC were prescribed in 56%, 21%, 15% and 8% of

Table I. Baseline patient and treatment characteristics (N = 2132)[a]

Characteristic	Value
Age, y	60.8 ± 11.9
Female, n (%)	1053 (49)
Body weight, kg	85.5 ± 14.5
Body mass index, kg/m^2	29.7 ± 5.1
Disease characteristics	
Systolic blood pressure, mmHg	158.5 ± 17.5
Diastolic blood pressure, mmHg	93.6 ± 9.8
Heart rate, beats/min	74.9 ± 10.0
Hypertension severity,[b] n (%)	
Normal/high normal blood pressure	140 (7)
Grade 1	711 (33)
Grade 2	927 (43)
Grade 3	354 (17)
Associated diseases, n (%)	
Coronary artery disease	725 (34)
Coronary artery disease with previous PCI	61 (3)
Coronary artery disease with previous CABG	29 (1)
Left ventricular hypertrophy	734 (34)
Angina pectoris	345 (16)
Myocardial infarction	174 (8)
Stroke or transient ischaemic attack	164 (8)
Peripheral arterial disease	123 (6)
Carotid artery stenosis	96 (5)
Cardiovascular risk factors, n (%)	
Family history of hypertension	1784 (84)
Dyslipidaemia	1494 (70)
Family history of coronary artery disease	1052 (49)
Smoking	515 (24)
Type 2 diabetes mellitus	500 (23)
Treatments, n (%)	
ACE inhibitors	1636 (77)
Calcium channel blockers	1262 (59)
β-Blockers	700 (33)
Cholesterol and triacylglycerol regulators	707 (33)
Antiplatelet therapy	640 (30)
Thiazide diuretics	330 (15)
Coronary therapy	312 (15)
Centrally acting antihypertensives	279 (13)
Nitrates	213 (10)
Angiotensin receptor blockers	105 (5)

a Linear variables are expressed as mean ± standard deviation.

b Severity was defined according to the 2007 hypertension guidelines of the European Society of Cardiology/European Society of Hypertension.[2]

ACE = angiotensin-converting enzyme; **CABG** = coronary artery bypass graft; **PCI** = percutaneous coronary intervention.

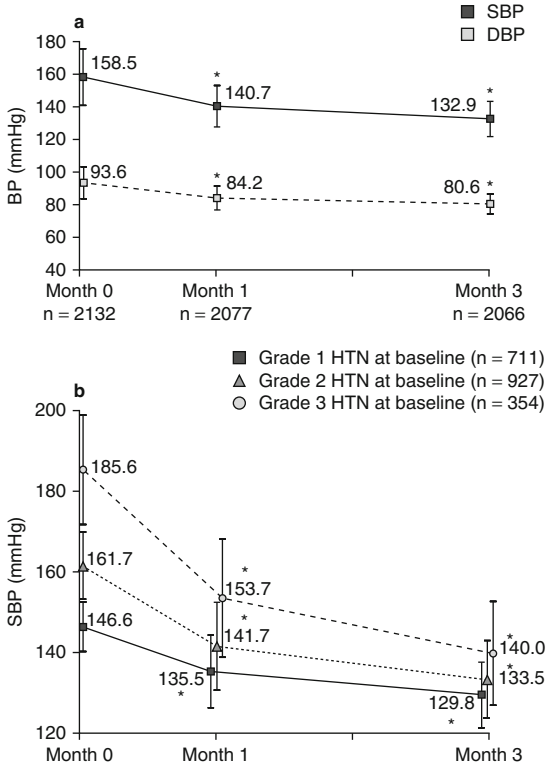

Fig. 1. BP after 1 month and 3 months of treatment with perindopril/amlodipine. (**a**) SBP and DBP in the entire cohort; (**b**) SBP by grade of hypertension. The three grades of hypertension were defined according to the 2007 European Society of Hypertension/European Society of Cardiology hypertension guidelines.[2] Means and standard deviations are reported; analysis was performed in the intent-to-treat population. In figure 1a numbers of patients for SBP are shown on the x-axis; numbers of patients for DBP are the same ± 5 patients. In figure 1b numbers in the key correspond to the number of patients in each subgroup at baseline. **BP** = blood pressure; **DBP** = diastolic BP; **HTN** = hypertension; **SBP** = systolic BP. * $p < 0.0001$ vs baseline.

patients, respectively. At month 1, perindopril/amlodipine 5 mg/5 mg, 10 mg/5 mg, 10 mg/10 mg and 5 mg/10 mg were prescribed in 51%, 23%, 17% and 9% of patients, respectively. At month 3, perindopril/amlodipine 5 mg/5 mg, 10 mg/5 mg, 10 mg/10 mg and 5 mg/10 mg were prescribed in 44%, 25%, 21% and 10% of patients, respectively.

Mean ± SD SBP/DBP decreased significantly and progressively over the treatment period with mean changes from baseline of −17.7 ± 14.6/−9.4 ± 8.8 mmHg after 1 month of treatment and of −25.5 ± 16.5/−12.9 ± 9.7 mmHg after 3 months ($p < 0.0001$; figure 1a). At the end of the study, mean ± SD SBP/DBP was 132.9 ± 10.6/80.7 ± 6.2 mmHg. Mean changes in SBP and DBP were statistically significant regardless of the dose of perindopril/amlodipine; mean changes in SBP varied from −24.4 ± 18.3 to −27.8 ± 15.9 mmHg and in DBP from −11.5 ± 11.1 to −14.3 ± 9.3 mmHg ($p < 0.0001$).

SBP (figure 1b) and DBP decreased significantly and progressively regardless of baseline hypertension. In patients with grade 1 hypertension, mean ± SD changes from baseline in SBP/DBP were −11.1 ± 9.3/−6.3 ± 6.7 mmHg after 1 month and −16.8 ± 9.4/−8.8 ± 7.2 mmHg after 3 months ($p < 0.0001$). In patients with grade 2 hypertension, mean ± SD changes from baseline in SBP/DBP were −20.0 ± 11.5/−11.1 ± 8.0 mmHg after 1 month and −28.3 ± 11.5/−15.1 ± 7.9 mmHg after 3 months ($p < 0.0001$). In patients with grade 3 hypertension, mean ± SD changes from baseline in SBP/DBP were −32.0 ± 17.8/−14.5 ± 11.1 mmHg after 1 month and −45.4 ± 16.4/−20.0 ± 11.5 mmHg after 3 months ($p < 0.0001$).

The number of patients who reached their target blood pressure increased with perindopril/amlodipine treatment (figure 2). Target blood pressure was reached by 51% of patients after 1 month of treatment and by 74% of patients after 3 months of treatment. When the data were analysed accord-

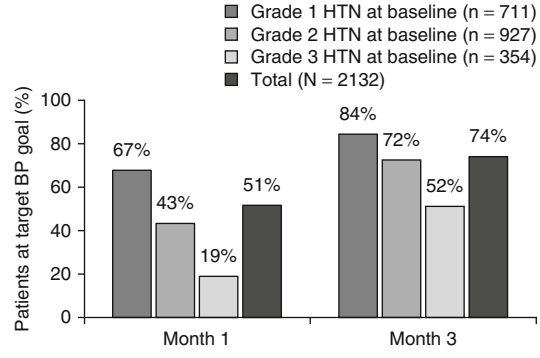

Fig. 2. Percentage of patients reaching target BP over time by grade of hypertension. Target values and severity groups were defined according to the 2007 European Society of Hypertension/European Society of Cardiology hypertension guidelines.[2] Target BP was defined as SBP/DBP <140/90 mmHg or <130/80 mmHg for patients with type 2 diabetes mellitus or with high cardiovascular risk. Analysis was performed in the intent-to-treat population. Numbers correspond to the number of patients in each subgroup at baseline. Patients who were at target BP at baseline (n = 140) are not depicted. **BP** = blood pressure; **DBP** = diastolic BP; **HTN** = hypertension; **SBP** = systolic BP.

ing to baseline severity, the number of patients reaching the target blood pressure increased progressively in each subgroup. Eighty-four percent, 72% and 52% of patients with grade 1, grade 2 and grade 3 hypertension, respectively, achieved blood pressure normalization after 3 months of treatment.

Decreases in Blood Pressure According to Risk Factors and Previous Treatments

Significant decreases in mean blood pressure were noted in patients with a history of stroke/transient ischaemic attack, myocardial infarction and type 2 diabetes (figure 3a). In addition, mean SBP and mean DBP decreased significantly with perindopril/amlodipine FDC regardless of the baseline treatment (figure 3b; $p < 0.0001$ vs baseline). At the end of the study, a significant reduction in mean ± SD SBP/DBP versus baseline of −28.8 ± 16.5/−13.6 ± 10.0 and of −25.3 ± 15.8/13.2 ± 8.9 mmHg was registered in patients previously uncontrolled by CCBs (n = 246) and ACE inhibitors (n = 616), respectively. Among patients previously treated with an ACE inhibitor/CCB free or fixed combination, mean ± SD blood pressure reductions of 23.9 ± 16.4/13.2 ± 8.9 mmHg were noted. In patients previously treated with an ACE inhibitor/amlodipine, the mean ± SD decrease from baseline in SBP/DBP was −23.8 ± 15.7/−12.3 ± 9.4 ($p < 0.0001$ vs baseline). When patients previously treated with trandolapril/amlodipine, ramipril/amlodipine, lisonipril/amlodipine or quinapril/amlodipine were considered separately, statistically significant changes from baseline were noted for each combination (figure 3c).

Heart Rate

Mean ± SD heart rate decreased significantly between baseline and 1 month from 74.9 ± 9.9 beats/min to 72.1 ± 7.8 beats/min ($p < 0.0001$) and between baseline and 3 months from 74.9 ± 9.9 beats/min to 70.6 ± 7.4 beats/min ($p < 0.0001$).

Safety and Tolerability

Treatment with perindopril/amlodipine FDC was well tolerated. One patient discontinued treatment after 1 month of treatment due to asthenia.

After 3 months of treatment, the most frequently observed treatment-emergent adverse events were ankle oedema (5.4% of patients), dyspnoea (1.8% of patients), headache (1.2% of patients), cough (1% of patients) and vertigo (1% of patients). One patient discontinued treatment after 1 month of treatment due to asthenia. No serious adverse events were reported.

The number of patients suffering from amlodipine-related ankle oedema decreased from 163 of 1085 (15%) patients treated with amlodipine at baseline to 86 of 1085 (7.9%) patients after 1 month of perindopril/amlodipine treatment to 68 of 1085 (6.3%) patients after 3 months of treatment (58% decrease from baseline, $p < 0.001$).

In the subgroup of 17 patients included into the study with controlled hypertension but with symptoms suggestive of intolerance to previous treatment (ankle oedema [n = 7], headache [n = 4], palpitations [n = 4], asthenia [n = 4] and backache [n = 1]), side effects resolved in 14 patients. Headache (n = 1), palpitations (n = 1) and backache (n = 1) were still reported by three patients. Oedema was not reported in any of these patients.

Discussion

In SYMBIO – a 3-month, open-label, longitudinal, phase IV study – optimization of treatment with perindopril/amlodipine FDC resulted in clinically and statistically significant decreases in blood pressure in patients with insufficient hypertension control and/or poor tolerance to previous therapy with an ACE inhibitor and/or a CCB. Significant changes in blood pressure were recorded regardless of baseline severity and baseline treatment. Blood pressure targets were reached by 74% of the overall patient population, 84% of patients with grade 1 hypertension, and 52% of patients with grade 3 hypertension. Treatment was well tolerated and was associated with a 58% reduction in the number of patients with amlodipine-related ankle oedema.

The blood pressure data presented herein are consistent with the data reported in the STRONG (SafeTy and efficacy analysis of coveRsyl amlodipine in uncOntrolled and Newly diaGnosed hypertension) trial. Here, after 3 months of treatment

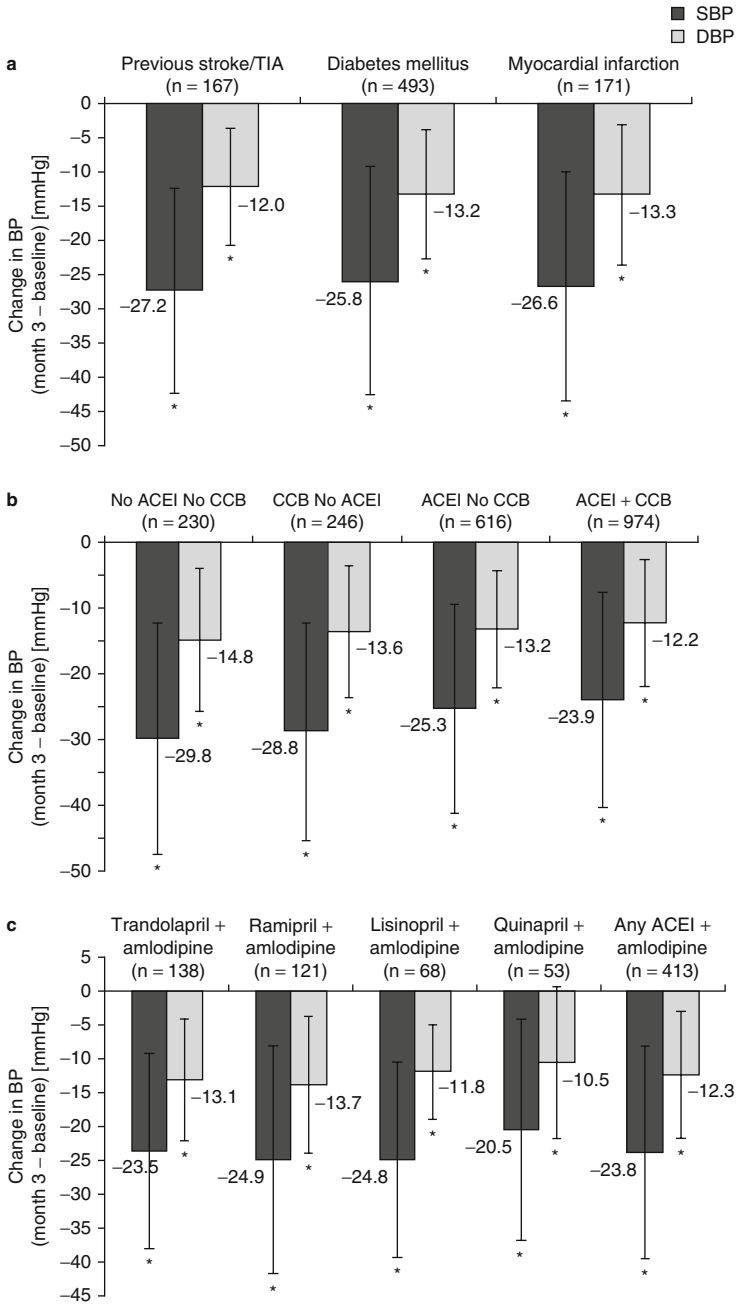

Fig. 3. Mean ± standard deviation changes in BP according to cardiovascular risk factors and baseline treatments. (**a**) Stroke/TIA, type 2 diabetes mellitus, myocardial infarction; (**b**) previous ACEI and/or CCB treatment; (**c**) previous ACEI/amlodipine treatment. In figure 3a, analysis was performed in the intent-to-treat population; in figures 3b and c analysis was performed in the final cohort. Numbers of patients for SBP are reported; numbers for DBP are the same ± 3 patients. **ACEI** = angiotensin-converting enzyme inhibitor; **BP** = blood pressure; **CCB** = calcium channel blocker; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; **TIA** = transient ischaemic attack. * $p < 0.0001$ vs baseline.

with perindopril/amlodipine, SBP/DBP decreased by a mean ± SD of 25.5 ± 16.5/–12.9 ± 9.7 mmHg. In the STRONG study in which 33% of patients had not been previously treated for hypertension, the blood pressure results with the perindopril/amlodipine combination were even more pronounced with mean decreases in SBP/DBP after 2 months of treatment of 41.9/23.2 mmHg.[17] In addition, when similar patient populations were considered, the normalization rates reported herein were consistent with those reported in the STRONG study in which 68% of patients uncontrolled on monotherapy and 60% of patients inadequately managed on combination therapy reached blood pressure targets with perindopril/amlodipine treatment.[17]

The importance of timely blood pressure control for long-term cardiovascular health is well understood.[18] In our study, clinically and statistically significant reductions in blood pressure were noted as early as 1 month after the optimization of treatment with perindopril/amlodipine FDC. In particular, for patients with severe hypertension, the mean ± SD 32.0 ± 17.8/–14.5 ± 11.1 mmHg drop in blood pressure after 1 month of perindopril/amlodipine treatment suggests a potential significant decrease in cardiovascular morbidity and mortality.

Furthermore, data from a previously reported long-term study suggest that long-term benefits would result from treatment with perindopril/amlodipine FDC. In the ASCOT-BPLA trial,[7] 5 years of treatment with amlodipine/perindopril led to statistically significant decreases in cardiovascular mortality (24%), stroke (23%), total cardiovascular events and procedures (16%), heart failure (16%), total coronary events (13%) and all-cause mortality (11%) compared with treatment with atenolol/bendroflumethiazide.[7] Thus, in the long term, patients treated with perindopril/amlodipine FDC would be expected to benefit from improvements in cardiovascular morbidity and mortality associated with blood pressure reduction as well as from perindopril/amlodipine-specific effects on cardiovascular health.

In the current study, in which 77% of patients were treated with an ACE inhibitor or an ACE inhibitor/CCB combination prior to inclusion, replacement of baseline ACE inhibitor/amlodipine treatments by fixed-combination perindopril/amlodipine led to significant and additional decreases in blood pressure. These results could be explained by clinically relevant differences in the profile of different ACE inhibitors. Indeed, as ACE inhibitors have different pharmacokinetics and pharmacodynamics, efficacy and tolerability profiles are expected to be different. Perindopril, for example, has a well demonstrated 24-hour antihypertensive efficacy with a once-a-day schedule. With a high trough-to-peak ratio of 75–100%, perindopril has been shown to have 24-hour efficacy when added to the long-acting CCB amlodipine with its trough-to-peak ratio of 87%.[19]

One of the most useful and important clinical observations in our trial was the fact that the initial dose of perindopril/amlodipine FDC, which was based on severity of hypertension and concomitant morbidity, did not need to be adjusted in 88–96% of patients, thereby suggesting good tolerability and adherence. In particular, oedema, which was specifically asked about and looked for, was rarely reported and decreased by more than 50% compared with previous treatment with CCBs alone or in combinations. Indeed, perindopril, through inhibition of the RAAS, reduction of amlodipine-induced reflex sympathetic activity and post-capillary dilatation, would be expected to alleviate ankle oedema caused by calcium channel blockade.[5] Together these data suggest that in real-life practice, physicians will encounter good treatment adherence and little need to adjust the perindopril/amlodipine dosage.

Study Limitations

The study's open-label design signifies that the study was not designed to assess placebo effects and regression to the mean. Although the absolute decreases in blood pressure should be interpreted with caution as they were not adjusted for a placebo effect, it is important to note that such a design was chosen in order to reflect real-life conditions. Furthermore, the absence of a washout period suggests that residual effects of previous treatment would not be nullified before the switch to perindopril/amlodipine. The 34% oc-

currence of coronary artery disease in our cohort was based mainly on non-invasive clinical evaluations and might therefore be overestimated, since only 8% of patients had myocardial infarction and 4% underwent coronary revascularization. No long-term cardiovascular outcome data are presented in this study. Data from other studies only indirectly suggest that long-term benefits could result from treatment with perindopril/amlodipine FDC.

Conclusion

Data from the presented study demonstrate that in real-life clinical practice in Slovakia, perindopril/amlodipine FDC was highly effective and well tolerated while lowering blood pressure to recommended target levels in a wide range of patients with multiple risk factors and co-morbidities. Despite proven morbidity-mortality benefits of amlodipine/perindopril among at-risk hypertensive patients free from cardiovascular diseases,[18] additional long-term studies specific to perindopril/amlodipine FDC would be needed to show that the decreases in blood pressure observed in our study translate into reduction in cardiovascular morbidity and into improvement in survival among patients. Nevertheless, perindopril/amlodipine data presented herein combined with extensive existing data describing amlodipine and perindopril suggest that perindopril/amlodipine FDC is a highly effective and easy to use long-term treatment option for arterial hypertension.

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