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ORIGINAL RESEARCH

# Efficacy and Tolerability of Fixed-Dose Combination Perindopril/Indapamide in Hypertensive Patients with a History of Stroke or Transient Ischemic Attack: PICASSO Trial

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## ABSTRACT

***Introduction***: In everyday medical practice, physicians often need to manage patients whose blood pressure is not well controlled. Those with a history of cerebrovascular disease are a high-risk group in need of rapid blood pressure control.

***Methods***: The PICASSO study was a real-life, observational trial involving 9257 inadequately treated hypertensive patients who were switched from previous therapy to the fixed-dose combination of perindopril 10 mg/indapamide 2.5 mg (PI) for 3 months. A subanalysis of data of 1117 hypertensive patients who met the clinical criteria of previous stroke or transient ischemic attack was performed. Twenty-four hour ambulatory blood pressure measurements (ABPMs) were also done in a small group of patients ($n$:38).

***Results***: At baseline, mean systolic/diastolic blood pressure (SBP/DBP) was 161.5 ± 15.2/93.1 ± 9.9 mmHg. After 1 month with the fixed dose of PI, average office SBP/DBP decreased to 140.0 ± 11.9/83.5 ± 7.7 mmHg. After 3 months, SBP/DBP had dropped to 132.9 ± 9.8/80.0 ± 6.2 mmHg, by 28.6 ± 15.5/13.1 ± 10.0 mmHg ($p < 0.001$). Blood pressure control rate (< 140/90 mmHg) was 67.3% after 3 months. When data were stratified by baseline blood pressure, decreases in SBP/DBP were statistically significant in patients with all grades (1–3) of hypertension. In patients previously treated with an angiotensin-converting enzyme inhibitor ± hydrochlorothiazide ($n = 677$), blood pressure decreased by 29.8 ± 15.5/13.3 ± 10.2 mmHg ($p < 0.001$). Decreases in 24-h ABPM values were also significant ($n = 38$). Treatment was well tolerated; only a few adverse events were recorded.

***Conclusion***: This study suggests that fixed combination perindopril 10 mg/indapamide 2.5 mg is an effective and well-tolerated treatment for patients with a history of stroke or transient ischemic attack.

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**Keywords:** Ambulatory blood pressure monitoring; Cardiology; Combination treatment; Hypertension; Indapamide; Perindopril; Stroke

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## INTRODUCTION

Hypertension is the strongest risk factor for cerebrovascular events as 51% of strokes worldwide are attributable to high systolic blood pressure (SBP) [1, 2]. Every 10 mmHg increase in home SBP is associated with a 30% increase in the risk of stroke [3]; every 20 mmHg increase in SBP leads to a doubling of the risk of mortality from stroke [4]. Treatment-induced decreases in blood pressure, however, have been shown to reduce the risk of stroke significantly, by 32%, in a large study of elderly patients with isolated systolic hypertension [5].

Patients with a history of stroke or transient ischemic attack (TIA) are at even higher risk with the 5-year risk of recurrent stroke being estimated at around 18% [6]. The 2013 European guidelines emphasize the importance of reducing blood pressure to below 140/90 mmHg in this patient population [7].

Among antihypertensive therapies, the combination of perindopril and indapamide seems particularly well suited for the treatment of patients with a history of stroke or TIA. The combination of this long-acting angiotensin-converting enzyme (ACE) inhibitor and the metabolically neutral thiazide-like diuretic not only meets the requirements for effectively lowering blood pressure in a wide range of patients, but also has been shown to reduce the risk of primary and secondary stroke [5, 8–13]. In the HYVET trial, for instance, very elderly patients with a wide range of comorbidities were treated with indapamide ± perindopril for 1.8 years. This treatment resulted in significant decreases in blood pressure and also a significant reduction in the rate of stroke (by 32%) and rate of death from stroke (by 39%) [5, 13]. In the PROGRESS study in hypertensive and non-hypertensive patients with a history of stroke or TIA, 4 years of treatment with a combination of perindopril/indapamide decreased blood pressure by an average of 12/5 mmHg, the risk of having a fatal or non-fatal secondary stroke by 43%, and the risk of having a major vascular event by 40% [10].

To investigate the blood pressure-lowering benefits of treatment with perindopril/indapamide in patients with a history of stroke or TIA in everyday conditions, a subanalysis of the large, open-label, observational Perindopril Plus Indapamide Combination Blood Pressure Reduction (PICASSO) trial [14] was performed. Hemodynamic and cardiometabolic parameters were determined in these patients who were switched from previous unsuccessful antihypertensive treatments to fixed-dose perindopril 10 mg/indapamide 2.5 mg for 3 months.

## METHODS

This retrospective analysis of the data of patients involved in the PICASSO trial was performed in the subgroup of patients with a history of stroke or TIA. Patients were identified by physicians based on medical history and adequate medical records. As previously described [14], the PICASSO study ($N = 9257$) was a Hungarian open-label observational study, which was designed to produce data in real-life conditions. Patients whose blood pressure (BP) was not controlled (BP > 140/90 mmHg) by previous angiotensin-converting enzyme (ACEI) or angiotensin receptor blocker (ARB) and diuretic (DIU) therapy were switched to treatment with the fixed-dose combination perindopril 10 mg/indapamide 2.5 mg (Coverex AS® Komb Forte, EGIS Pharmaceuticals Plc, Budapest, Hungary) [15, 16] at the discretion of their physician. This change of treatment was in line with the previously planned therapeutic approach. The only two protocol-specified elements were office visits at baseline, 1 month, and 3 months after the initiation of perindopril/indapamide combination. The measurement of office blood pressure and heart rate with a validated oscillometric manometer was performed at these visits and, if necessary, more frequently at the treating physicians' discretion. The option to initiate ambulatory blood pressure monitoring (ABPM) using a validated device (MEDITECH ABPM, Hungary), decision to test biochemical parameters, and decision to add or maintain additional antihypertensive treatments and other types of drugs (e.g., statins, aspirin) were not specified in the protocol and were left to the treating physicians. All patients

signed informed consent prior to enrollment in the study. The Ethics Committee of the Hungarian Medical Research Council [TUKEB no. 8-34812009-1018EKU (866/PII09.)] approved the protocol. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Descriptive statistics were used to summarize data. Target office blood pressure was defined as $< 140/90$ mmHg according to the 2013 European Society of Hypertension/European Society of Cardiology hypertension guidelines [7]. Mean levels of biochemical parameters were calculated at baseline and at 3 months. Adverse events were recorded at 1 and 3 months. Chi squared tests were used to compare data at baseline and at 3 months. Significance was set at $p < 0.05$.

## RESULTS

This subanalysis of the PICASSO study included data of 1117 hypertensive patients with a history of stroke or TIA. These patients were enrolled and treated with perindopril/indapamide because of their uncontrolled blood pressure (in 67.2%), their fluctuating blood pressures (in 38.0%), and the side effects of previous drugs (in 7.7%).

Mean age of patients was 70.3 ± 9.9 years. Risk factors and concomitant diseases included age > 55 years in 83.1%, ischemic heart disease in 47.8%, obesity in 47.6%, left ventricular hypertrophy in 44.7%, type 2 diabetes mellitus in 25.7%, smoking in 20.0%, known peripheral artery disease in 17.9%, and chronic renal disease in 8.1% of patients. The ratio of risk factors and comorbidities was significantly higher than in the total study population (Table 1). Time since the previous cerebrovascular event was not recorded. Mean duration of known hypertension was 14.6 ± 8.5 years. Ninety-six percent of patients were treated for hypertension by different drugs, including ACEI ± hydrochlorothiazide (HCTZ) (60.6%), beta-blockers (61.3%), calcium channel blockers (50.9%), diuretics in monotherapy (37.2%), and angiotensin receptor blockers (ARB) ± HCTZ (9.0%).

At baseline, mean systolic (SBP)/diastolic blood pressure (DBP) was 161.5 ± 15.2/93.1 ± 9.9 mmHg. The SBP was significantly higher than the mean value of the total study population (158.9 ± 14.3/93.0 ± 9.4 mmHg). Three hundred twenty-two patients had grade 1 hypertension (28.8%), the majority (595) of patients had grade 2 hypertension (53.3%), and 200 patients had grade 3 hypertension (17.9%). At baseline, mean heart rate was 79.0 ± 10.0 bpm.

After switching to treatment with perindopril/indapamide previous ACEIs, ARBs, and diuretics other than indapamide were stopped. Beta-blockers and calcium channel blockers continued to be prescribed in 62.0% and 42.5% of patients, respectively, but the doses might have been changed according to the decision of the treating physician.

### Blood Pressure and Heart Rate

One month after the start of treatment with perindopril/indapamide, mean office SBP/DBP decreased to 140.0 ± 11.9/83.5 ± 7.7 mmHg (Fig. 1a). At 3 months, blood pressure further decreased to 132.9 ± 9.8/80.0 ± 6.2 mmHg resulting in a significant average drop in SBP/DBP by 28.6 ± 15.5/13.1 ± 10.0 mmHg ($p < 0.001$). The blood pressure control rate was 67.3% at 3 months. Heart rate also decreased significantly to 73.3 ± 6.7 bpm (changed by 5.7 ± 9.4 bpm; $p < 0.001$) at 3 months.

Data were stratified by baseline BP. Decreases in office SBP/DBP were directly related to the baseline BP and were statistically significant in all three groups (Fig. 1b): by 19.2 ± 9.3/8.4 ± 7.8 mmHg for patients with grade 1 hypertension, by 29.5 ± 10.4/14.0 ± 8.4 mmHg for patients with grade 2 hypertension, and by 46.9 ± 16.2/20.7 ± 11.5 mmHg for patients with grade 3 hypertension. When data were stratified according to the previous antihypertensive treatment by an RAS blocker (ACEI or ARB) + a diuretic (Fig. 1c), in patients previously treated with an ACEI ± HCTZ ($n = 677$), the office BP decreased significantly from 162.1 ± 15.3/93.0 ± 10.3 to 132.3 ± 9.5/79.7 ± 6.2 mmHg,

**Table 1** Baseline characteristics in the cerebrovascular disease subanalysis of the PICASSO trial

| | **Subgroup** ***N*** **= 1117** | **Total population** ***N*** **= 9683** |
|---|---|---|
| Demographic parameters | | |
| Male, % | 43.2% | 46% |
| Age in years, mean ± SD | 70.3 ± 9.9 | 61.8 ± 12.1 |
| Cardiovascular risk factors[a] | | |
| Age (> 55 years), *n* (%) | 928 (83.1%) | 5550 (57.3%) |
| Dyslipidemia, *n* (%) | 674 (60.3%) | 4747 (49.0%) |
| Obesity, *n* (%) | 532 (47.6%) | 4673 (48.3%) |
| Family history, *n* (%) | 435 (38.9%) | 3763 (38.9%) |
| Smoking, *n* (%) | 223 (20.0%) | 2898 (29.9%) |
| Pre-diabetes (5.6–6.9 mmol/l), *n* (%) | 135 (12.1%) | 1159 (12.0%) |
| Associated comorbidities[a] | | |
| Ischemic heart disease, *n* (%) | 534 (47.8%) | 2799 (28.1%) |
| Diabetes, *n* (%) | 287 (25.7%) | 2100 (21.7%) |
| Peripheral vascular disease, *n* (%) | 200 (17.9%) | 945 (9.8%) |
| Chronic heart failure, *n* (%) | 172 (15.4%) | 654 (6.8%) |
| Renal disease, *n* (%) | 91 (8.1%) | 393 (4.1%) |
| Target organ damage[a] | | |
| Atherosclerosis, *n* (%) | 715 (64.0%) | 2649 (27.4%) |
| Left ventricular hypertrophy, *n* (%) | 499 (44.7%) | 2786 (28.8%) |
| Microalbuminuria, *n* (%) | 121 (10.8%) | 588 (6.1%) |
| Elevated serum creatinine level, *n* (%) | 119 (10.7%) | 434 (4.5%) |
| Grade of hypertension[b] | | |
| Grade 1, *n* (%) | 322 (28.8%) | 3205 (33.1%) |
| Grade 2, *n* (%) | 595 (53.3%) | 4550 (47.0%) |
| Grade 3, *n* (%) | 200 (17.9%) | 1204 (12.4%) |
| Previous antihypertensive therapy[a] | | |
| ACE inhibitor ± HCTZ, *n* (%) | 677 (60.6%) | 4706 (48.6%) |
| Beta-blocker, *n* (%) | 685 (61.3%) | 4356 (45.0%) |
| Calcium channel blocker, *n* (%) | 568 (50.9%) | 3398 (35.1%) |
| Diuretic in monotherapy, *n* (%) | 416 (37.2%) | 2183 (22.5%) |
| Angiotensin receptor blocker ± HCTZ, *n* (%) | 100 (9.0%) | 669 (6.9%) |

**Table 1** continued

| | Subgroup $N = 1117$ | Total population $N = 9683$ |
|---|---|---|
| Other, *n* (%) | 0 (0%) | 448 (4.6%) |

*ACE* angiotensin-converting enzyme, *HCTZ* hydrochlorothiazide, *SD* standard deviation

[a] As reported on the case report form

[b] Determined from baseline office blood pressure and defined according to the 2013 European Society of Hypertension/European Society of Cardiology guidelines [7]

by 29.8 ± 15.5/13.3 ± 10.2 mmHg; ($p < 0.001$). In those patients previously treated with an ARB ± HCTZ ($n = 100$), office BP decreased from 161.6 ± 13.2/93.8 ± 8.6 to 133.8 ± 10.9/80.4 ± 6.9 mmHg, by 27.9 ± 15.0/13.5 ± 9.0 mmHg; ($p < 0.001$). Changes from baseline were also statistically significant (Table 2).

### Drugs for Comorbid Conditions, Safety, and Tolerability After Switching to Perindopril/Indapamide

Switching previous antihypertensive treatment to the fix combination of perindopril/indapamide had little effect on drug prescriptions for comorbidities (Table 3). Small but significant improvements were noted for several metabolic parameters (Fig. 2). Changes in total cholesterol from baseline after 3 months were − 0.7 ± 0.9 mmol/l ($p < 0.001$), for high density lipoprotein-cholesterol + 0.1 ± 0.3 mmol/l [$p$ = not significant (NS)], for low density lipoprotein-cholesterol − 0.5 ± 0.7 mmol/l ($p < 0.001$), for triglycerides − 0.1 ± 1.7 mmol/l ($p$ = NS), for fasting blood glucose − 0.4 ± 0.9 mmol/l ($p = 0.02$), for serum potassium − 0.1 ± 0.5 mmol/l ($p$ = NS), for serum sodium + 0.0 ± 6.0 mmol/l ($p$ = NS), for serum uric acid − 19.8 ± 52.6 µmol/l ($p$ = NS), and for serum creatinine − 2.7 ± 16.0 µmol/l ($p$ = NS).

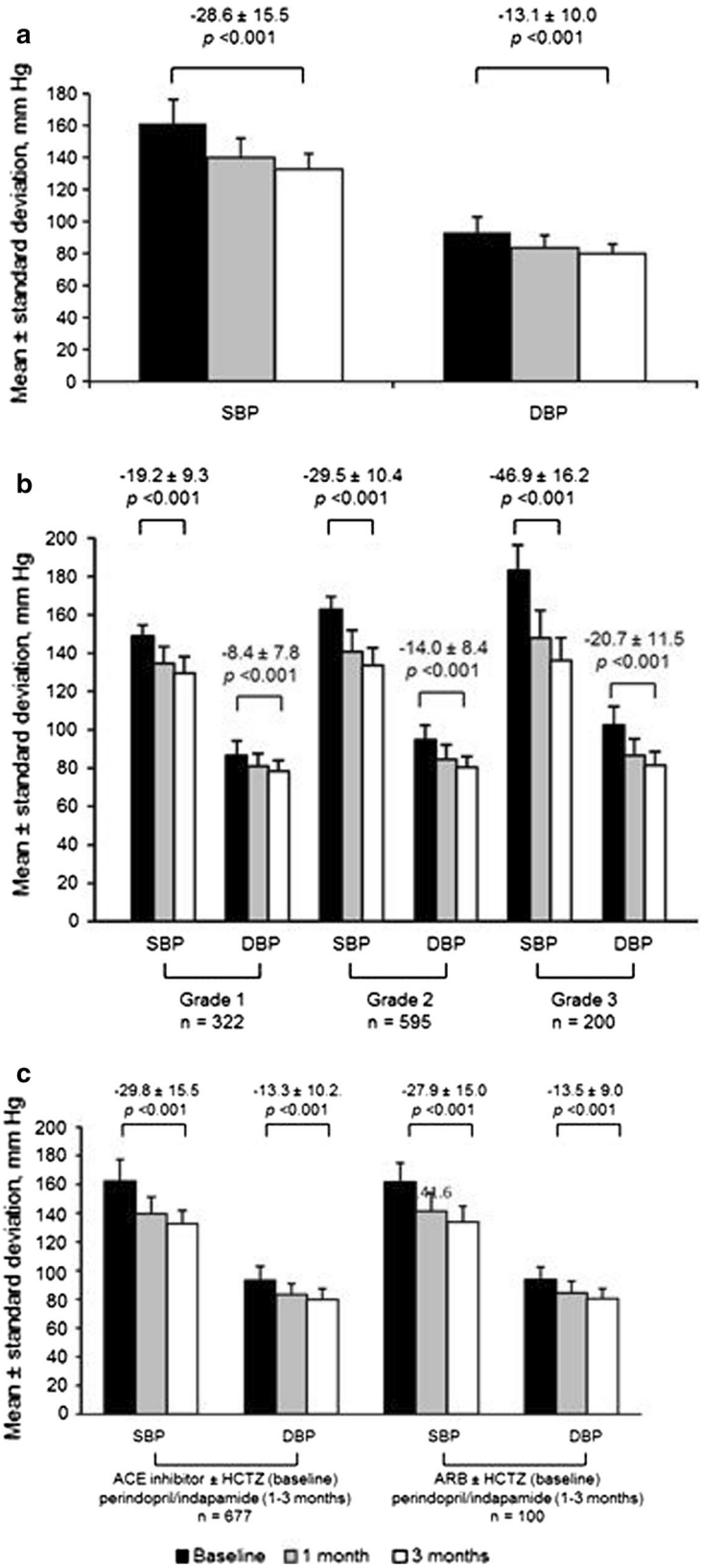
Treatment was well tolerated. Nineteen adverse events and three serious adverse events occurred. Dizziness was reported in five patients (0.4%), hypotension in four (0.4%), and cough in two (0.2%). Leg edema was reported only by one patient. The serious adverse events were minor stroke after surgery ($n = 1$) and transient ischemic attack ($n = 2$).

## DISCUSSION

As for secondary stroke or cerebrovascular prevention, very limited studies/results are available. The results of the Post-Stroke Antihypertensive Treatment Study (PATS) showed that in the therapy of patients with a previous cerebrovascular event ($n = 5665$), indapamide (2.5 mg/day) reduced the total risk of a secondary stroke by 30% to a significant extent ($p < 0.001$) during the 2-year follow-up period [17]. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial—included 6105 patients with previous stroke or TIA—the perindopril + indapamide combination therapy resulted in a significant reduction of recurrent stroke by 43%. It should be stressed that the number of both ischemic (− 36%) and hemorrhagic strokes (− 76%) showed a significant reduction [18]. Other studies have also shown that perindopril treatment improves cerebral vasomotor reactivity and cerebral perfusion reserve in patients with a history of stroke [19]. These effects may have contributed to the beneficial results of the PROGRESS trial.

The results of the PATS and PROGRESS studies, which produced positive outcomes, served as a basis for the most recent European (ESH/ESC 2013) and American (AHA/ASA, 2014) guidelines for secondary prevention of stroke, which primarily recommend diuretics in monotherapy or combined with ACE inhibitors for the antihypertensive treatment of patients who have undergone a cerebrovascular event [7, 20].

Thus, our data from the PICASSO trial with a combination of perindopril 10 mg/indapamide 2.5 mg are in line with and comparable (as far as


a
-28.6 ± 15.5
p <0.001
-13.1 ± 10.0
p <0.001
Mean ± standard deviation, mm Hg
SBP
DBP
b
-19.2 ± 9.3
p <0.001
-29.5 ± 10.4
p <0.001
-46.9 ± 16.2
p <0.001
-8.4 ± 7.8
p <0.001
-14.0 ± 8.4
p <0.001
-20.7 ± 11.5
p <0.001
Grade 1
n = 322
Grade 2
n = 595
Grade 3
n = 200
c
-29.8 ± 15.5
p <0.001
-13.3 ± 10.2
p <0.001
-27.9 ± 15.0
p <0.001
-13.5 ± 9.0
p <0.001
ACE inhibitor ± HCTZ (baseline)
perindopril/indapamide (1-3 months)
n = 677
ARB ± HCTZ (baseline)
perindopril/indapamide (1-3 months)
n = 100
Baseline
1 month
3 months

◀**Fig. 1** Decreases in office blood pressure over time with treatment with fixed-dose combination perindopril 10 mg/indapamide 2.5 mg. Blood pressure was measured at baseline and 1 and 3 months. *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *DBP* diastolic blood pressure, *HCTZ* hydrochlorothiazide, *SBP* systolic blood pressure. **a** Office blood pressure ($N = 1117$). **b** Office blood pressure according to baseline grade of hypertension. Grade of hypertension was defined according to ESH/ESC 2013 guidelines [7]. **c** Office blood pressure according to baseline antihypertensive treatment. Significance was set at $p < 0.05$

the BP-decreasing effects are concerned) to the results of previous trials (PATS, PROGRESS), support recent guidelines for secondary stroke prevention, and offer an effective alternative to existing but unsuccessful antihypertensive treatments by different agents. In the PATS study, the average BP was reduced by 5/2 mmHg because of administration of 2.5 mg indapamide (the average BP was 154/93 mmHg at randomization), and in the PROGRESS study the average BP was reduced by 12.5/5.0 mmHg in the 4/2.5 perindopril/indapamide combination group (at randomization, BP was 149/87 mmHg) [17]. In our substudy, the average BP was 149/87 mmHg in the grade I group, which was reduced by 19/8 mmHg because of 10/2.5 mg perindopril/indapamide combinations [21].

Although European guidelines do not recommend specific antihypertensive treatments for reducing blood pressure in patients with a history of stroke or TIA, our data suggest that switching patients to perindopril/indapamide may be an alternative approach to adding a third hypertensive drug to patients who are not controlled with an ACE inhibitor/HCTZ or an ARB/HCTZ. Moving away from treatments with HCTZ is also supported by at least one set of

**Table 3** Concomitant treatments in the cerebrovascular disease subanalysis of the PICASSO trial

| Concomitant treatments | Baseline $N = 1117$ | 3 months $N = 1117$ |
|---|---|---|
| Statin, *n* (%) | 887 (79.4%) | 867 (77.6%) |
| Acetylsalicylic acid, *n* (%) | 797 (71.4%) | 736 (65.9%) |
| Oral anti-diabetics, *n* (%) | 285 (25.5%) | 269 (24.1%) |
| Clopidogrel, *n* (%) | 199 (17.8%) | 181 (16.2%) |
| Insulin, *n* (%) | 82 (7.3%) | 76 (6.8%) |
| Fibrate, *n* (%) | 49 (4.4%) | 42 (3.8%) |
| Other, *n* (%) | 298 (26.7%) | 258 (23.1%) |

**Table 2** Blood pressure decreases after switching to treatment with fixed-dose combination perindopril 10 mg/indapamide 2.5 mg for 3 months: cerebrovascular disease subanalysis of the PICASSO trial

| Treatment prior to switch to per/ind | *N* | SBP in mmHg | | | DBP in mmHg | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 3 months of per/ind | Change from baseline | Baseline | 3 months of per/ind | Change from baseline |
| Enalapril ± HCTZ | 303 | 163.0 ± 15.7 | 131.6 ± 9.5 | − 31.4 ± 16.3[a] | 93.3 ± 10.5 | 79.5 ± 6.1 | − 13.8 ± 10.5[a] |
| Ramipril ± HCTZ | 119 | 161.1 ± 13.2 | 132.5 ± 9.3 | − 28.6 ± 14.2[a] | 93.1 ± 9.6 | 80.1 ± 6.2 | − 13.1 ± 9.2[a] |
| Irbesartan ± HCTZ | 13 | 161.9 ± 16.6 | 132.0 ± 12.2 | − 29.9 ± 14.1[a] | 95.2 ± 5.6 | 80.9 ± 7.2 | − 14.2 ± 6.9[a] |
| Valsartan ± HCTZ | 13 | 163.9 ± 11.4 | 127.3 ± 10.5 | − 36.5 ± 14.9[a] | 95.8 ± 7.0 | 77.9 ± 6.4 | − 17.9 ± 6.2[a] |
| Losartan ± HCTZ | 58 | 161.6 ± 13.1 | 135.9 ± 10.5 | − 25.7 ± 15.0[a] | 93.0 ± 9.4 | 81.6 ± 6.6 | − 11.5 ± 9.6[a] |

Data are expressed as mean ± standard deviation

*DBP* diastolic blood pressure, *HCTZ* hydrochlorothiazide, *per/ind* perindopril 10 mg/indapamide 2.5 mg, *SBP* systolic blood pressure

[a] $p < 0.001$

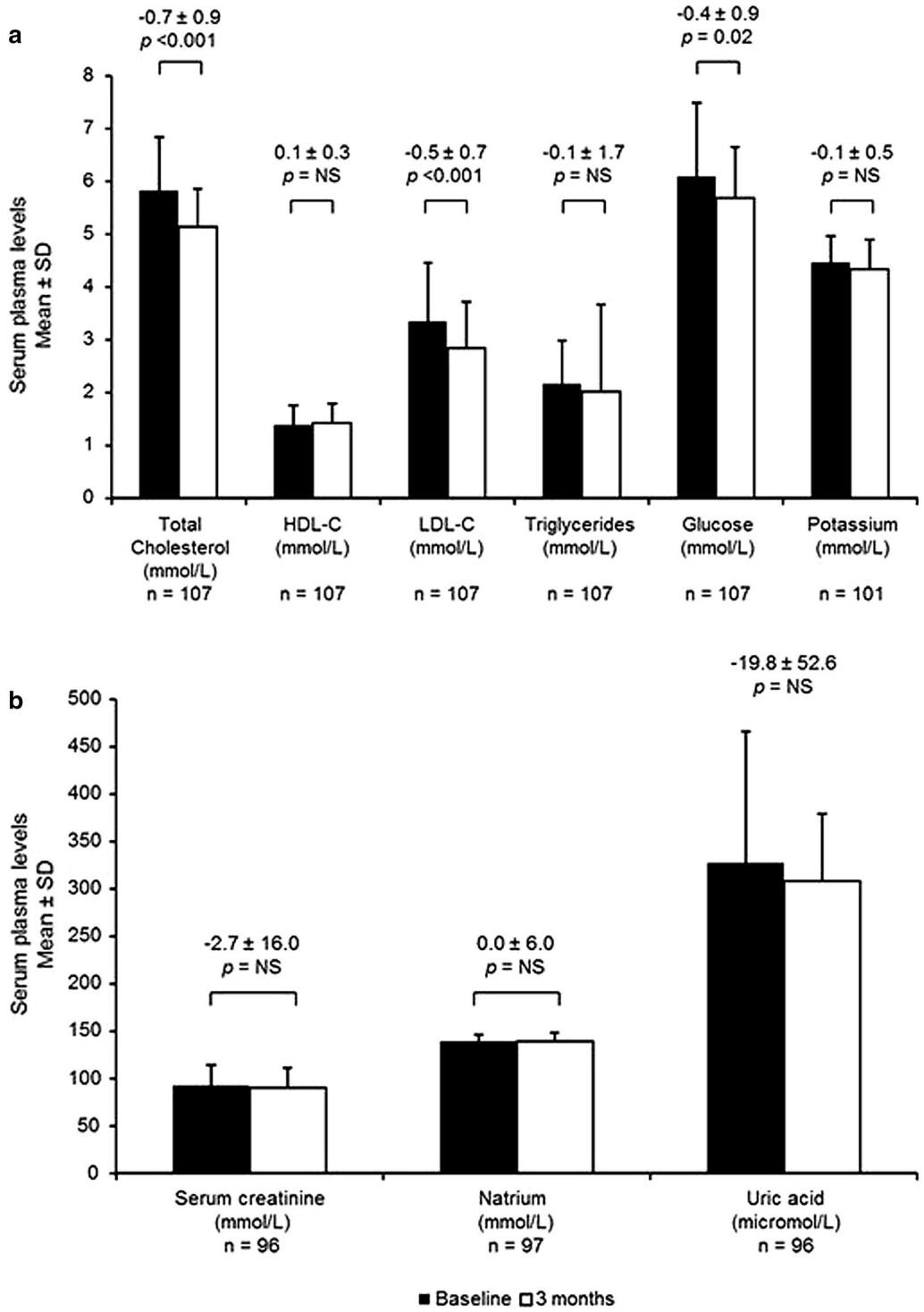



**Fig. 2** Metabolic parameters after 3 months of treatment with fixed-dose combination perindopril 10 mg/indapamide 2.5 mg. Measurement of metabolic markers was not specified in the protocol and was left to the treating physician's discretion. Significance was set at $p < 0.05$. *HDL-C* high density lipoprotein-cholesterol, *LDL-C* low density lipoprotein-cholesterol, *NS* not significant, *SD* standard deviation

guidelines. The British Society of Hypertension now recommends that indapamide and chlorthalidone be prescribed rather than HCTZ because of concerns about adverse metabolic effects associated with HCTZ treatment [22]. The American Hypertension Association also highlights the efficacy of indapamide treatment in its stroke prevention guidelines [20].

The perindopril/indapamide treatment was well tolerated with only few adverse events in our study. The data describing the effect of treatment on laboratory parameters are consistent with the fact that indapamide has been shown to be metabolically neutral and that treatment with combination perindopril/indapamide is well tolerated in a wide range of patients [8–13, 23].

### Study Limitations

As in all open-label observational trials, the placebo effect associated with enrolling in a prospective clinical trial cannot be evaluated. Concerns about placebo effects can be partially offset by the fact that the efficacy of combination perindopril/indapamide has been shown in many randomized-controlled trials [8–12] and that a systematic review of randomized-controlled trials in the Cochrane database showed that the placebo effect in hypertension may not be statistically significant [24]. Data describing metabolic parameters should be interpreted with caution as they are only available for 10% of patients.

The term "in line with the previously planned therapeutic approach" was not well defined and was left open to interpretation. The vagueness of this definition is consistent with our goal to collect data that are as directly relevant to everyday practice as possible. Few constraints were placed on the study physicians, and physicians were free to continue to manage their patients as they saw fit. We therefore cannot exclude the possibility that physicians enrolled more patients than they would have if the term had been more carefully defined or that some bias was introduced in patient selection.

## CONCLUSIONS

In everyday medical practice, physicians often need to decide how to manage hypertensive patients who are not responding adequately to their antihypertensive treatment. In patients with a history of stroke and TIA, a certain amount of urgency is associated with finding a successful treatment as the risk of recurrent stroke and other cardiovascular events is high. This study provides data that support switching patients to perindopril 10 mg/indapamide 2.5 mg, significant decreases in blood pressure and high control rates were recorded, and this treatment was well tolerated.

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***Authorship.*** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

***Disclosures.*** Csaba András Dézsi and Csaba Farsang have nothing to disclose.

***Compliance with Ethics Guidelines.*** All patients signed informed consent prior to

enrollment in the study. The Ethics Committee of the Hungarian Medical Research Council (TUKEB no. 8-34812009-1018EKU (866/PII09.) approved the protocol. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

***Data Availability.*** The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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