Original Article

Effect of the Angiotensin-Converting Enzyme Inhibitor Perindopril on 24-Hour Blood Pressure in Patients with Lacunar Infarction: Comparison between Dippers and Non-Dippers

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Antihypertensive therapy based on the angiotensin-converting enzyme (ACE) inhibitor perindopril reduced the incidence of recurrent stroke in the Perindopril Protection against Recurrent Stroke Study (PROGRESS). The present study assessed the effect of perindopril on the 24-h blood pressure (BP) in hypertensive patients with lacunar infarction using ambulatory BP monitoring (ABPM). There was a 4-week observation period, a 4-week treatment period 1 (perindopril at 2 mg/day), and a 4-week treatment period 2 (perindopril at 4 mg/day). Twenty-seven hypertensive patients with lacunar infarction (10 dippers and 17 non-dippers) were enrolled. The average 24-h BP values were significantly decreased after both treatment periods. When the patients were divided into dippers and non-dippers, perindopril exhibited a different BP-lowering effect in the groups with these two circadian BP patterns. In dippers, daytime BP was significantly decreased, whereas nighttime BP was not, so an excessive fall of nighttime BP was not observed. In non-dippers, both daytime and nighttime BP were decreased, with a stronger BP-lowering effect at night. There was a significant inverse correlation between the magnitude of the change in nighttime BP and the night/day ratio. These results suggested that perindopril could induce a sustained decrease of the 24-h BP in patients with lacunar infarction. In particular, a more pronounced nighttime BP-lowering effect was observed in non-dippers. As the incidence of non-dippers is reported to be high among patients with cerebrovascular disease, better nighttime BP control by perindopril might have helped to improve the outcome of such patients in PROGRESS. (*Hypertens Res* 2005; 28: 571–578)

***Key Words*: perindopril, hypertension, cerebrovascular disease, 24-hour blood pressure, non-dipper**

Introduction

In the recently published Perindopril Protection against Recurrent Stroke Study (PROGRESS), antihypertensive therapy based on the angiotensin-converting enzyme (ACE) inhibitor perindopril reduced the incidence of recurrent stroke in patients with a history of transient ischemic attacks or minor stroke (*1*). Moreover, additional beneficial effects associated with the blood pressure (BP) lowering by perindopril-based therapy, such as reductions in the incidence of subsequent silent infarcts (*2*), dementia (*3*), and disability (*4*), have been shown by a sub-study of PROGRESS. Furthermore, improvements of cerebral vasomotor reactivity (*5*) and cerebral perfusion reserve (*6*) by perindopril have been reported. Such beneficial effects of perindopril-based antihypertensive therapy may be attributed to BP reduction and/or additional effects that extend beyond the action on BP.

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Table 1. Baseline Characteristics

	Dippers (n=10)	Non-dippers (n=17)
Male	9	12
Female	1	5
Age	62±13	67±6
Office BP	162±12/89±16	156±8/85±7
24-Hour BP	149±8/85±7	150±12/86±9
Daytime BP	157±8/90±7	151±13/87±9
Nighttime BP	136±8/77±7	149±13/83±10
Antihypertensive agents		
No	5	5
Yes	5	12
Ca-blockers	4	10
Amlodipine (5 mg/day)	3	8
Benidipine (4 mg/day)	1	1
Manidipine (20 mg/day)	0	1
β-Blockers	0	2
Carteolol LA (15 mg/day)	0	2
Diuretics	0	1
Trichlormethiazide (1 mg/day)	0	1
α-Blockers	1	1
Doxazosin (2 mg/day)	1	1

BP, blood pressure.

PROGRESS was performed based on office BP data. Since the introduction of ambulatory BP monitoring (ABPM), it has been consistently reported that the extent of hypertensive target organ damage (*7*, *8*) and the incidence of subsequent cardiovascular events (*9*) are better correlated with the 24-h BP measured by ABPM than the office BP. Although there have been reports about the effect of perindopril on the 24-h BP in hypertensive patients (*10*, *11*), no study about the effect of perindopril on cerebrovascular disease has ever been reported. Therefore, we conducted the present study to assess the effect of perindopril on the 24-h BP in patients with lacunar infarcts, which represent a form of minor stroke.

Methods

Hypertensive patients with lacunar infarction were enrolled in this study between 1 month and 5 years after the event. Lacunar infarction was defined as occlusion of a perforating artery and was diagnosed when patients exhibited a lacunar syndrome and a deep small infarct less than 15 mm in diameter on magnetic resonance imaging (MRI). Patients who had large artery disease with ≥50% stenosis or embolic heart disease such as atrial fibrillation or ischemic heart disease were excluded. Patients were eligible for the study if they had an office BP ≥140/90 mmHg, when measured on at least two separate occasions. Untreated hypertensive patients with a office BP ≥160/95 mmHg, patients with unstable symptoms, those unable to attend our hospital outpatient department, and those using ACE inhibitors or angiotensin II receptor blockers during the previous 2 weeks were excluded. Patients with modification of the dosage of other antihypertensive medications during the previous 2 weeks were also excluded. The study protocol was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from all patients before enrollment.

The study consisted of a 4-week observation period, a 4-week treatment period 1 (treatment with perindopril at 2 mg once a day), and a 4-week treatment period 2 (perindopril at 4 mg once a day). Potentially eligible patients were enrolled in the observation period, and all patients underwent ABPM after the observation period. Patients with a mean 24-h BP ≥130/80 mmHg on ABPM (*12*) received perindopril at a dose of 2 mg once a day in treatment period 1. Throughout the observation period and the treatment period, antihypertensive medications that had been started before the observation period were continued without any changes. After treatment period 1, patients who tolerated perindopril at 2 mg daily continued into treatment period 2.

The office BP was measured with a mercury sphygmomanometer every 4 weeks with the patient seated after resting for 5 min. The ABPM was measured by the cuff-oscillometric method using an ABPM system (ABPM-630; Colin Corporation, Aichi, Japan). Blood pressure was monitored in either the left or right arm (the same arm throughout the study) at 30-min intervals from between 1:00 PM and 4:00 PM to the same time on the following day. All patients kept activity records to document the times at which they slept, walked, or took medications. The mean BP was calculated during the daytime period (between 6:00 AM and 10:00 PM) and the nighttime period (between 10:30 PM and 5:30 AM), and the night/day ratio was also calculated. Patients with a night/day ratio of less than 0.9 were defined as dippers and the remaining patients were defined as non-dippers. Then the patients were divided into a dipper group and a non-dipper group. The office BP, 24-h BP, and circadian rhythm of BP before and after treatment were compared between the two groups. The relationship between the magnitude of change in the 24-h BP due to treatment and the baseline night/day ratio was also examined.

Statistical Analysis

Data are presented as the mean±SD. Differences between the two groups were analyzed by the unpaired Student's t-test, χ^2 test, or Fisher's exact probability test. Data obtained before and after treatment were analyzed by the paired Student's t-test, and values of $p<0.05$ were considered statistically significant. For analysis of correlations, Pearson's correlation coefficients were determined.

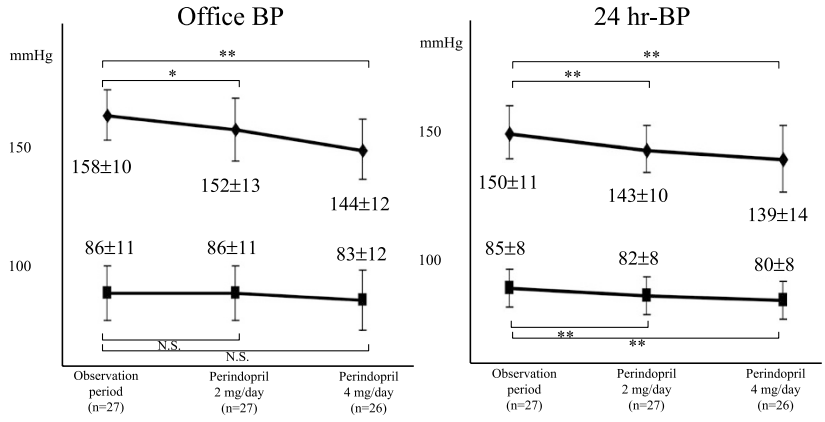

Fig. 1. *Effect of perindopril on the office blood pressure and 24-h blood pressure. Values are the mean±SD.* *p < *0.01,* **p < *0.001 (paired* t*-test). BP, blood pressure; N.S., not significant.*

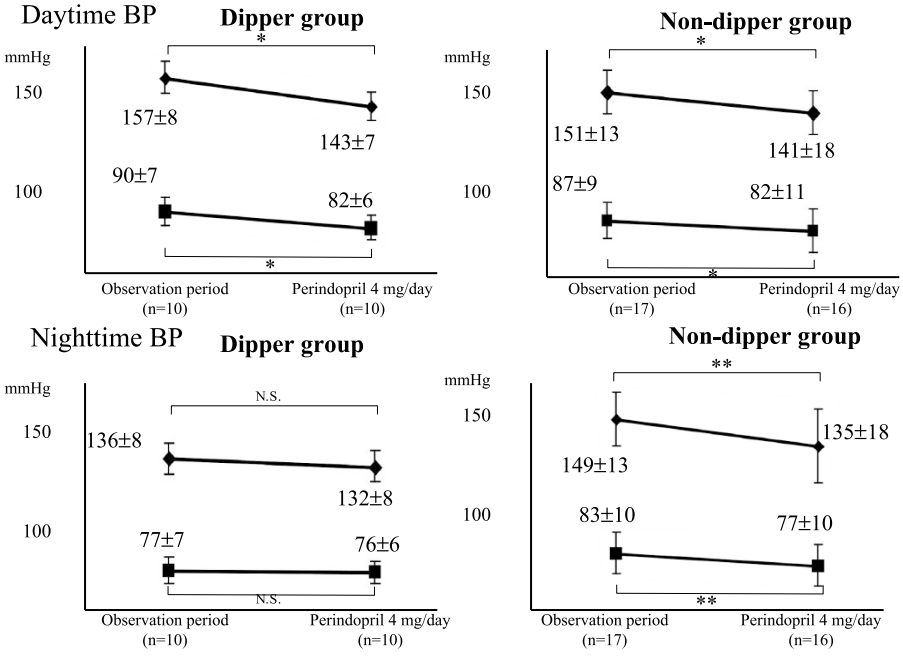

Fig. 2. *Effect of perindopril on the daytime and nighttime blood pressure. Values are the mean±SD.* *p < *0.01,* **p < *0.001 (paired* t*-test). BP, blood pressure; N.S., not significant.*

Results

Characteristics of the Patients

Thirty-five patients were enrolled in the observation period, but eight patients were ineligible to enter the treatment period because of a mean 24-h BP < 130/80 mmHg after the observation period. The other 27 patients (10 dippers and 17 non-dippers) met the inclusion criteria. One patient did not undergo 24-h blood pressure monitoring on completion of treatment period 2 and so was excluded from analysis of the data for that treatment period 2. None of the patients complained of sleep disturbance due to monitoring throughout the study. Their demographic data, office BP, 24-h BP, and antihypertensive treatment status are shown in Table 1.

Effect of Perindopril on Office BP and 24-h BP

In all subjects, the office systolic BP was significantly decreased after both treatment periods 1 and 2. The average 24-h systolic and diastolic BP values were also significantly decreased after both treatment periods (Fig. 1). In the dipper group, daytime systolic and diastolic BP were significantly

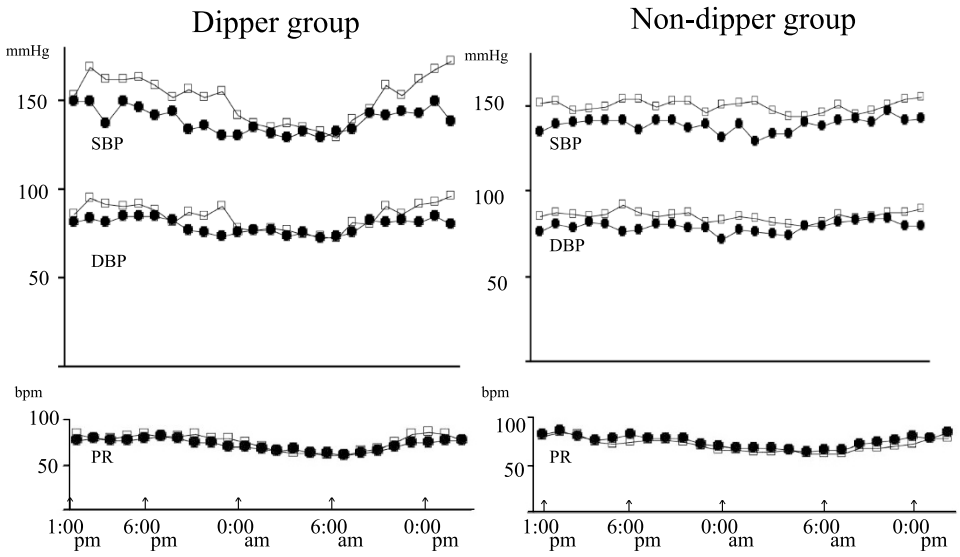

Fig. 3. *Circadian blood pressure patterns of the dipper and non-dipper groups. Closed circles show perindopril (4 mg/day) and open squares show the observation period. SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.*

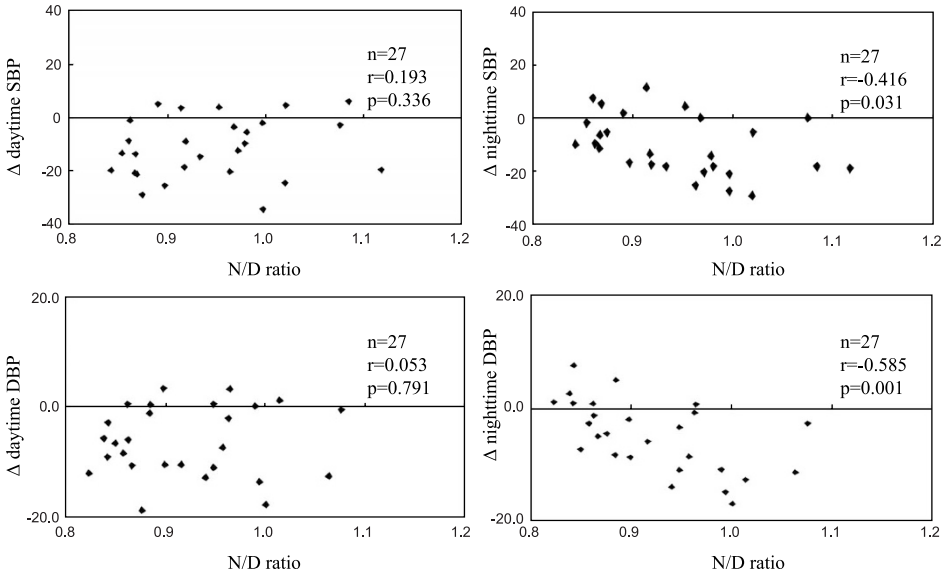

Fig. 4. *Correlations between Δ blood pressure and the baseline night/day ratio. SBP, systolic blood pressure; DBP, diastolic blood pressure;* N/D *ratio, night/day ratio.*

decreased after treatment period 2, but nighttime BP was not changed by treatment. In the non-dipper group, daytime systolic and diastolic BP were significantly decreased after period 2. The nighttime systolic and diastolic BP were also significantly decreased after period 2. The magnitude of the decrease was greater for nighttime BP than daytime BP (Fig. 2).

The circadian BP patterns of the two groups are depicted in Fig. 3. In the dipper group, the daytime BP was clearly decreased, whereas the nighttime BP was unchanged. In the non-dipper group, on the other hand, BP was decreased throughout the 24-h period and the decrease was greater during the nighttime than during the daytime.

The correlation between the magnitude of change in the daytime or nighttime BP with treatment and the baseline night/day ratio is displayed in Fig. 4. There was a significant inverse correlation between the change of the nighttime systolic or diastolic BP and the night/day ratio.

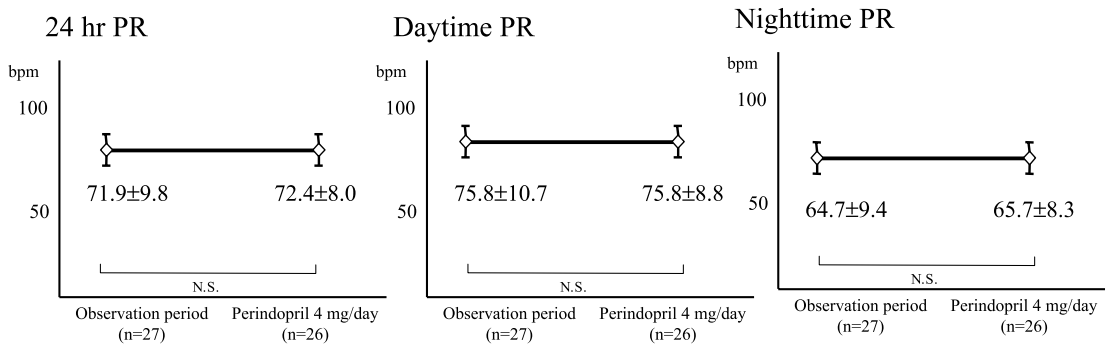

Fig. 5. *Effect of perindopril on the 24-h pulse rate, daytime pulse rate, and nighttime pulse rate. Values are the mean±SD. PR, pulse rate; N.S., not significant.*

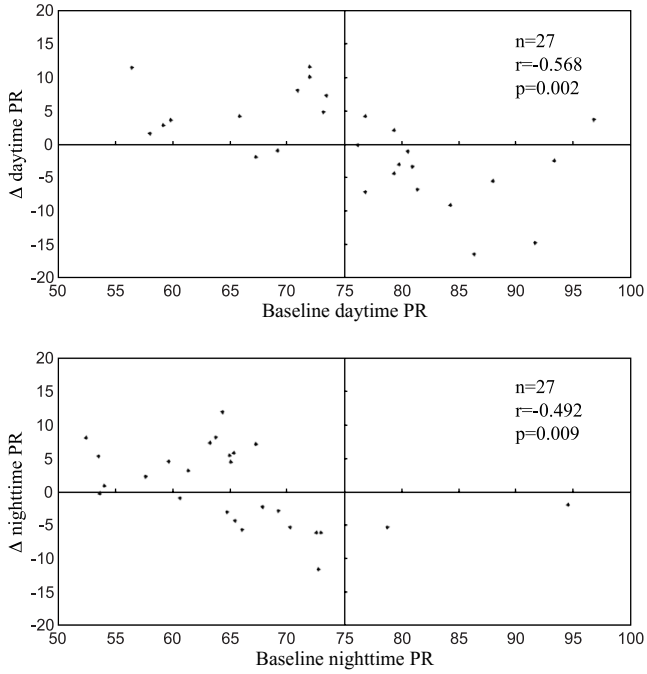

Fig. 6. *Correlation between Δ PR and the PR during the observation period. PR, pulse rate.*

Effect of Perindopril on the 24-h Pulse Rate

Administration of perindopril did not cause a significant change of the 24-h pulse rate, daytime pulse rate, or nighttime pulse rate throughout the treatment period (Fig. 5). Nonetheless, the actual alteration of the pulse rate (*Δ* PR) after administration of perindopril exhibited an inverse correlation with the pulse rate during the observation period (Fig. 6).

Safety

In this study, there was only one adverse drug reaction detected, which was an increase of the uric acid level. None of the patients complained of cough throughout the study.

Discussion

The present study showed that treatment with perindopril (4 mg once daily in the morning) in hypertensive patients with lacunar infarction had a differential effect on the 24-h BP for two different circadian BP patterns, *i.e.*, dippers and non-dippers. Daytime BP was significantly decreased in dippers, but nighttime BP was not, and an excessive fall of nighttime BP was not observed. Among the non-dippers, 70% had already been treated with other long-acting antihypertensive agents and had not shown an adequate decrease of nighttime BP, but perindopril reduced both daytime and nighttime BP, with the nocturnal decline being more pronounced. As the night/day

ratio increased, the magnitude of the decrease in nighttime BP with perindopril treatment became greater. This means that perindopril was especially effective for lowering the nighttime BP in non-dippers. It has been reported that perindopril has a high trough/peak ratio and a long-acting antihypertensive effect (*13*, *14*). Perindopril was also reported to be particularly effective for nocturnal hypertension by Morgan and Anderson (*15*), but ours is the first clinical study in which 24-h ABPM was performed on hypertensive patients with lacunar infarction receiving perindopril therapy who were divided into dippers and non-dippers. It has been reported that twice daily administration of an α1 blocker (doxazosin) (*16*) or an αβ blocker (arotinolol) (*17*) had BP-lowering effects similar to those of perindopril, but there have been few reports about once daily therapy as used in this study. In a study of amlodipine and nisoldipine, the 24-h BP was monitored and these two medications were shown to reduce the nighttime blood pressure of both dippers and non-dippers (*18*). Thus, a more pronounced reduction of nighttime BP in non-dippers treated once daily in the morning may be a specific action of perindopril.

The lack of a nocturnal BP decline in BP, *i.e.*, non-dipper status, has been related to more severe hypertensive target organ damage and increased cardiovascular risk independently of the 24-h BP (*19–24*). In the Systolic Hypertension in Europe (Syst-Eur) trial, non-dipper status was associated with a higher incidence of subsequent cardiovascular events (*21*). In the Ohasama study (*22*), each 5% decrease in the decline in nocturnal BP was associated with an approximately 20% greater risk of cardiovascular mortality. We previously reported that non-dipper status was significantly associated with subsequent recurrence of stroke and/or progression of vascular dementia in patients with lacunar infarcts (*23*, *24*).

O'Brien *et al*. (*25*) reported that patients with non-dipper hypertension showed a higher incidence of stroke than dippers. The percentage of non-dippers (defined as a decrease of nocturnal BP by $<10\%$) among our 200 lacunar infarct patients was 77.5% (*26*), which is quite different from the percentage of 31.8% in a large international database of normotensive and hypertensive patients (*27*). Thus it can be presumed that the prevalence of non-dippers would have been high in PROGRESS (*1*). Accordingly, the stronger BP-lowering effect of perindopril on the nighttime BP of non-dippers might have exerted a more beneficial effect on the prevention of recurrent stroke and dementia than would have been expected from the office BP. Interestingly, administration of diuretics to patients with salt-sensitive hypertension has been reported to convert the diurnal BP pattern from non-dipper to dipper (*28*). It can thus be assumed that the combination of perindopril and a diuretic in PROGRESS preferentially lowered the nighttime BP, leading to a decrease in the incidence of recurrent stroke.

The precise pathogenetic mechanisms responsible for the lack of a dip in BP remain uncertain. Alterations of autonomic function, such as blunted diurnal changes of sympathetic and parasympathetic activity (*29*), sodium-sensitive essential hypertension (*30*), insulin resistance (*31*), genetic factors (*32*), physical activity (*33*), and peripheral vascular resistance (*34*), may all contribute to the development of non-dipper status.

The mechanism by which perindopril preferentially lowered the nighttime BP and modulated the pulse rate in the present study is not clear, but these findings are consistent with results reported by Yasuda *et al*. (*10*) in 24 patients with diabetic nephropathy. They used power-spectral analysis to demonstrate that administration of perindopril reduced sympathetic activity during sleep, and such an effect could provide a plausible explanation for our results. ACE inhibitors are considered to reduce norepinephrine release by decreasing the angiotensin-II concentration (*35*). Moreover, ACE inhibitors also prevent the breakdown of bradykinin, which releases cerebral vasodilators such as prostacyclin synthetase and nitric oxide (*36*). Furthermore, it is suggested that BP becomes angiotensin II-dependent during sleep (*11*, *37*). It thus can be presumed that perindopril may have an especially marked effect on nighttime BP. These multiple actions might contribute to the reduction of nighttime BP in non-dippers.

Recently, chronobiological therapy involving the administration of antihypertensive agents at bedtime has been highlighted. In the Heart Outcomes Prevention Evaluation (HOPE) trial (*38*), an ACE inhibitor (ramipril) was given once daily at bedtime and more pronounced BP lowering during the night was achieved. Administration of valsartan at bedtime also reduced the incidence of non-dippers (*39*). In the present study, once daily administration of perindopril in the morning produced a similar effect on the diurnal BP pattern in non-dippers. A study to assess the effect of normalizing the circadian BP pattern should be performed in the near future.

The present study had the following limitations. Patients were administered perindopril but none of the patients were additionally treated with a diuretic, so the design was not exactly the same as that of PROGRESS. Despite this, the documentation of 24-h BP control by perindopril alone at least supports the good outcome of the active treatment group in PROGRESS.

In conclusion, perindopril induced a sustained decrease of the 24-h BP in hypertensive patients with lacunar infarction. In particular, a more pronounced nighttime BP-lowering effect was observed in non-dippers. As the incidence of non-dippers is increased among patients with cerebrovascular disease, better nighttime BP control by perindopril might have contributed to improving the outcome of patients receiving active treatment in PROGRESS.

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