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Effective end-organ protection in arterial hypertension: possibilities of third-generation calcium antagonists

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ABSTRACT

Objective: Arterial hypertension (AH) is one of the most common and socially significant diseases worldwide. Despite years of experience gained in studying hypertension, the problems concerning selection of antihypertensive therapy with pleiotropic organ-protecting effects are still of current importance. The purpose of the study was to assess therapeutic efficacy and pleiotropic organ-protective capability of third-generation calcium antagonist lercanidipine in patients with stage 2-3 hypertension.

Method: Our study enrolled a total of ninety-two 31-to-84-year-old patients. Of these, 72 patients diagnosed as having stage 2 or 3 AH composed the Study Group and 20 apparently healthy subjects were included into the Control Group. At baseline and after 6 months, all patients of the Study Group underwent examinations consisting in measuring biochemical parameters [total cholesterol (TCH), triglycerides (TG), low-density lipoprotein cholesterol (LDL CH), uric acid, urea, creatinine, glucose], 24-hour ambulatory BP monitoring, echocardiography (EchoCG) in order to assess the dimensions and volume of the cardiac chambers, thickness of the left ventricular posterior wall (LVPW) and left-ventricular myocardium mass index (LVMMI), studying microalbuminuria (MAU) , a known marker of endothelial dysfunction and early renal lesion; assessing the state of the vascular wall by the ankle-brachial index (ABI) and pulse pressure (PP). Antihypertensive therapy consisted in lercanidipine alone taken at a dose of 10-20 mg/day, failure to thereby achieve the target BP level was followed by additionally prescribing an angiotensin converting enzyme (ACE) inhibitor, enalapril, given at a dose of 5-20 mg twice daily.

Results: All patients by the end of the study achieved the target level of AP ($p<0.05$), also demonstrating significantly improved ($p<0.01$) parameters of endothelial dysfunction and an early marker of renal damage (MAU), indices of elastic properties of the vascular wall ABI ($p<0.05$) and PP ($p=0.01$). Significantly positive dynamics was observed for the following parameters: decreased creatinine concentration ($p<0.001$), increased GFR ($p<0.001$), decreased levels of TCH ($p<0.01$) and LDL CH ($p<0.001$).

Conclusion: Lercanidipine therapy of patients with stage 2 - 3 AH proved highly efficient, well tolerated, metabolically neutral with pleiotropic organ-protecting properties in the form of improved condition of the vascular wall, correction of endothelial dysfunction, nephroprotective action.

Keywords: arterial hypertension, lercanidipine, third-generation calcium antagonist, pleiotropic effects

INTRODUCTION

Despite success of world medicine in discovering the mechanisms of the development of AH, its possible complications, emergence of novel drugs for antihypertensive therapy, AH still remains one of the most common and socially significant diseases worldwide. According to the findings of population-based epidemiological studies, 40% of adult population suffer from AH (1), the prevalence of AH amongst the elderly increases to 60 – 70% (2), 30 – 40% of patients are aware of their diseases and not more than 10% receive and strictly adhere to the adjusted antihypertensive therapy (3). Long-term uncontrolled AH leads to serious and life-threatening complications such as stroke, myocardial infarction, end-stage renal disease (ESRD), dementia. Initial stages of the development of these complications are target-organ damages with subclinical manifestations (left ventricular myocardium hypertrophy, elevation of PP > 60 mm Hg, decreased ABI < 0.9, MAU, cognitive impairments) (4). While managing hypertensive patients, special attention should be paid both to home control of AP and carrying out examination aimed at early diagnosis of the initial target-organ damage, including determination of the parameters of MAU, ABI, PP, 24-h BP monitoring (in order to assess the circadian profile of AP), EchoCG (for assessment of initial structural alterations of the heart. Detecting initial signs of target-organ

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damage in such patients should immediately be followed by prescribing antihypertensive therapy with a possibility of versatile protection of target organs. To a promising group of drugs capable of accomplishing this mission belong third-generation calcium channel antagonists.

The study was aimed at assessing therapeutic efficacy and pleiotropic organ-protective potential of third-generation calcium antagonist lercanidipine in patients with class 2-3 AH.

MATERIALS AND METHODS

This prospective six-month cohort study enrolled a total of ninety-two 31-to-84-year-old patients. Of these, 72 patients diagnosed with stage 2-3 AH (25 men and 47 women, mean age 66.3±12.1 years) composed the Study Group and the Control Group consisted of 20 apparently healthy people (6 men and 14 women, mean age 58.8±5.6 years).

All patients underwent general clinical examination including taking case history, assessment of the subjective status, determining the office level of AP, biochemical blood count with determination of lipid spectrum (levels of TCH, TG, LDL CH), uric acid, glucose; determination of the renal filtration ability (concentration of urea and creatinine) with the calculation of the glomerular filtration rate according to the CKD-EPI formula. Microalbuminuria (MAU) was assessed as a marker of endothelial dysfunction and early renal damage. The structure of cardiac chambers was determined by means of visual methodology of EchoCG to assess the following parameters: thickness of the left ventricular posterior wall (LVPW), interventricular septum (IVS), left ventricle myocardium mass index (LVMMI). The state of the vascular wall was evaluated using the ABI and PP. Efficacy of antihypertensive therapy was assessed by means of 24-hour ambulatory blood pressure monitoring, the target values were the daytime level of systolic AP (SAP) below 135 mm Hg, diastolic AP (DAP) – 85 mm Hg, nighttime SAP values below 120 mm Hg, DAP – 70 mm Hg. We also evaluated the dynamics of the AP level by the data of a blood pressure self-monitoring (BPSM) diary at weeks 2 and 4 of treatment.

Seven days after discontinuation of the previously taken antihypertensive therapy (the wash-out period) we prescribed and titrated lercanidipine at a dose of 10 – 20 mg/day, assessing at the follow-up visits the efficacy of treatment by the parameters of the BPSM. Failure to achieve the target level of AP 135/85 mm Hg on monotherapy according to the BPSM data was followed by additionally prescribing ACE inhibitor enalapril at a starting dose of 5 mg twice daily, subsequently increasing the dose to 40 mg/day (maximum).

The exclusion criteria were as follows: side effects of the drug, acute cardiovascular diseases or decompensation of chronic diseases. All patients enrolled into the programme of follow-up successfully completed the study, with no side reactions observed.

The data was statistically processed using the SPSS software package version 23. Statistical significance of differences of the means between the groups for independent samples were analysed using the Student's t-test and 95% confidence interval (95% CI), to compare the values differing from the normal distribution we used the Mann-Witney test. The results were regarded as statistically significant if $p \leq 0.05$. The mean values and standard deviation were used to describe quantitative parameters.

Table 1 shows the findings of the clinical examination of the Control and Study Groups prior to treatment, demonstrating that the groups were comparable by gender and age. The parameters of the Study group patients significantly differed from those of the Control Group patients, thus suggesting that AH is an independent risk factor for the development of left ventricular myocardial dystrophy, endothelia dysfunction, renal lesion, increased rigidity of the vascular wall, and in combination with impaired lipid spectrum is a powerful predictor of the development of atherosclerosis of various-localization vessels.

Table 1: *Baseline clinical characteristics of the Study and Control Group patients*

Parameter	Study Group, n = 72	Control Group, n = 20
Men	25 (35%)	30 (30%)
Women	47 (65%)	14 (70%)
Age, years	66±12	58,8±5,6
Urea, mmol/L	8.3±3.7	5.895±1.09**
Creatinine, μmol/L	123.7±79.3	82.7±10.18**
Blood glucose, mmol/L	5.1±1.9	4.72±0.65
Uric acid, mcmol/L	369.8±105.2	328.85±68.76
TCh, mmol/L	5.56±1.5	4.95±0.86
TG, mmol/IL	1.95±1.4	1.304±0.38***
LDLP CH, mmol/IL	2.9±0.9	2.05±0.9**
MAU, mg/mmoL	28.97±61.55	0.74±0.27**
IVS, mm	12.88±3.9	9.14±1.18**
LVPW, mm	13.1±16.9	8.65±1.56**
LVMMI, g/m^2	156.13±61.1	95.4±11.3**
ABI	0.92±0.11	0.95±0.05***
Mean daytime SAP, mm Hg	148±7.4	124±10.4**
Mean daytime DAP, mm Hg	94.5±5.95	75.25±8.36**
Mean nighttime SAP, mm Hg	129.3±6.21	107.4±11.35**
Mean nighttime DAP, mm Hg	81.1±5.6	62.25±7.28**
Mean nighttime SAP, mm Hg	140.6±5.73	126.95±7.94**
Mean circadian DAP, mm Hg	87±5.35	81.1±5.82**
PP, mm Hg	53.5±5.38	46.25±4.32**
Morning home SAP, mm Hg	169.3±15.6	122.75±7.34**
Morning systolic DAP, mm Hg	96.2±11.16	73±8.18**
Evening home SAP, mm Hg	169.1±40.57	121.15±6.08**
Morning home DAP, mm Hg	93.96±11.1	70±7.07**

Note: ** p≤0.001, *** p≤0.05 as compared with the Control Group.

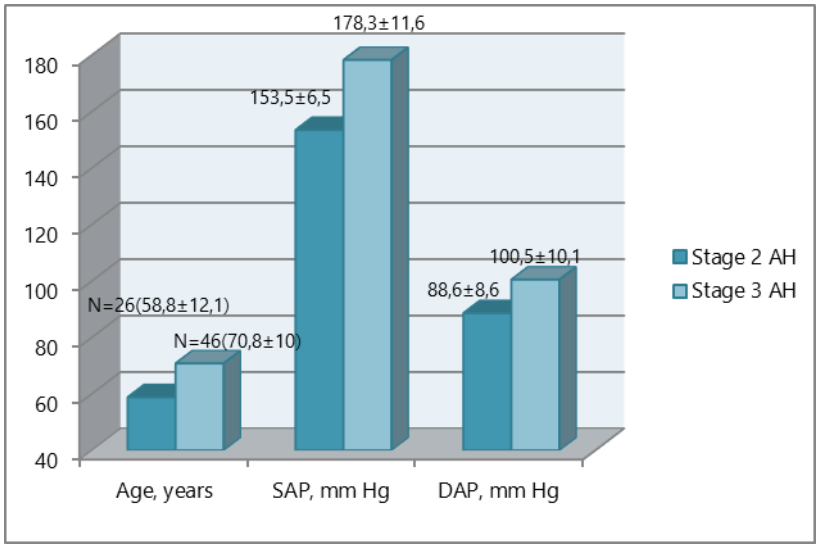

Figure 1: *Parameters of age and levels of home AP in patients with stage 2 and stage 3 AH*

RESULTS

The Study Group appeared to predominantly consist of patients suffering from stage 3 AH – 46 (63.9%), with the remaining 26 (36.1%) patients suffering from stage 2 AH. **Figure 1** shows the age-related incidence of stage 2 AH and stage 3 AH, demonstrating that the latter was encountered more often in elderly people, which increases the risk of target-organ damage and the development of serious cardiovascular complications.

The findings of 24-hour blood pressure monitoring in patients with stage 2 AH yielded the following results: mean circadian SAP amounted to 137.9±4.56 mm Hg, DAP – 84.5±5.3 mm Hg, mean daytime value SAP/DAP 141.7±3.81/90.4±2.9 mm Hg, mean nighttime SAP/DAP 124.6±3.93/75.8±4.9 mm Hg. The stage 3 AH patients

Table 2: *Distribution of patients by the presence of associated clinical conditions*

Associated clinical conditions, number of patients	Men n (%)	Women n (%)	Stage 2 AH n (%)	Stage 3 AH n (%)
Ischaemic heart disease, n = 45	18 (40%)	27 (60%)	13 (29%)	32 (71%)
Chronic kidney disease, n = 24	11 (46%)	13 (54%)	7 (29%)	17 (71%)
Previously endured acute impairment of cerebral circulation, n = 9	1 (11%)	8 (89%)	-	9 (100%)
Type 2 diabetes mellitus, n = 17	3 (18%)	14 (82%)	2 (12%)	15 (88%)

Table 3: *Dynamics of AP levels in the Study Group patients as a whole on the background of antihypertensive therapy at weeks 2 and 4 according to the BPSM data*

Parameter, mm Hg	At week 2	At week 4	p
Home SAP, morning	149.6±18.7	135.3±9.9	<0.001
Home SAP, evening	147.9±15.9	134.9±10.7	<0.001
Home DAP, morning	88.5±15.9	81.1±8.1	<0.001
Home DAP, evening	87±8.8	81.7±7.4	<0.001

demonstrated the following values: mean circadian SAP was 142.1±5.82 mm Hg, DAP 88.5±4.86 mm Hg, mean daytime SAP/DAP 151.5±5.56/96.8±5.96 mm Hg, mean nighttime SAP/DAP 131.9±5.69/84.1±8.77 mm Hg (**Figure 1**).

The distribution of patients by the associated clinical conditions is shown in **Table 2**, demonstrating that a severe degree of AH was significantly more often encountered in patients with associated clinical conditions, which automatically refers these patients to the group of a very high risk for the development of AH complications.

After the wash-out period, all patients of the Study Group were assigned to receive third-generation calcium antagonist lercanidipine as an antihypertensive agent. The average dose of the drug at week 2 of treatment amounted to 17.8±4.2 mg/day, at week 4 to 18.3±3.75 mg/day, and by the end of the study the patients took the drug at a dose of 18.3±3.75 mg/day. Failure to achieve the target level of AP with lercanidipine alone was followed by additionally prescribing enalapril. The average dose of the latter amounted at week 2 to 18.4±5.54 mg/day, at week 4 to 24.4±10.46 mg/day and by the end of the study to 26.4±10.6 mg/day. Taking into consideration_account the dose titration, 50% of patients at week 2 and 88% of patients at week 4 were found to have the target levels of AP (**Table 3**), with 33 (45.8%) patients receiving lercanidipine as monotherapy, and 39 (54.02%) as a component of combined therapy. Mention should also be made that 100% of patients adhered to keeping their BPSM diaries.

With a high degree of significance by the end of the study, according to the findings of the 24-h BP monitoring and blood pressure self-monitoring (BPSM) diaries all patients achieved the target level of AP not exceeding 135/85 mm Hg. The level of the mean circadian value of SAP in the Study Group at 6 months after the beginning of treatment amounted to 122.5±5.4 mm Hg, with the mean circadian DAP amounting to 71±7.05 mm Hg **(Table 4)**. This confirmed high antihypertensive efficacy of lercanidipine in treatment of patients with stage 2 and 3 AH both as monotherapy and as a component of combined therapy.

Table 4: *Parameters of 24-h BP monitoring, PP and ABI at baseline and at 6 months of therapy*

Parameter	At baseline [95% CI]	At 6 months of therapy [95% CI]	p
Mean daytime SAP, m Hg	148±7.4 [146.3-149.7]	124±9.6 [121.8-126.3]	<0.001
Mean daytime DAP, mm Hg.	94.5±5.95 [93.1- 95.9]	77.4±13.3 [74.3-80.43]	<0.001
Mean nighttime SAP, mm Hg	129.3±6.21 [127.8-130.7]	109.3±10.2 [106.9-111.6]	<0.001
Mean nighttime DAP. Mm Hg	81.1±5.6 [79.1-83.1]	62.9±8 [61.1-64.7]	<0.001
Mean circadian SAP, mm Hg	140.6±5.73 [139.2-141.9]	122.5±5.4 [121.2-123.7]	<0.001
Mean circadian DAP, mm Hg	87±5.35 [85.8-88.3]	71±7.05 [69.4-72.6]	<0.001
PP, mm Hg	53.5±5.38 [52.3-54.8]	51.4±5.83 [50.1-52.8]	<0.01
Morning home SAP, mm Hg	169.3±15.6 [165.7-172.9]	128.8±9.3 [126.6-130.9]	<0.001
Morning home DAP, mm Hg	96.2±11.16 [93.6-98.8]	78.8±11.4 [76.2-81.4]	<0.001
Evening home SAP, mm Hg	169.1±40.57 [159.7-178.5]	127.8±10.5 [125.3-130.2]	<0.001
Evening home DAP, mm Hg	93.96±11.1 [91.4-96.5]	78.7±10.3 [76.3-81.1]	<0.001
ABI	0.92±0.11 [0.92-0.97]	0.95±0.12 [0.89-0.94]	<0.005

Table 5: *Dynamics of biochemical parameters of blood and MAU initially and at 6 months of treatment*

Parameter	At baseline	At 6 months
Urea, mmol/L	8.31±3.75*	8.07±3.62*
Creatinine, μmol/L	123.74±79.3**	114.75±75.8**
Blood glucose, mmol/L	5.11±1.95*	5.26±1.52*
Uric acid, mmol/L	369.83±105.29*	373.69±87.37*
TCH, mmol/L	5.56±1.46***	5.04±0.72***
TG, mmol/L	1.95±1.36*	1.82±1.17*
LDL CH, mmol/L	2.91±0.91**	2.41±0.7**
MAU, mg/mmoL	28.97±61.55***	19.03±52.06***
GFR (SKD-EPI), mL/min/1.73m^2	46.4±15.3**	51.4±17.7**

Note: * - statistically insignificant; ** - statistically significant p≤0.001; *** - statistically significant p≤0.01, as compared with the baseline values.

As can be seen from **Table 4**, by the end of the study with a high degree of significance also noted was improvement of the parameters of the vascular wall rigidity. Thus, the ABI decreased by 3% and PP by 4% from the baseline levels, thereby suggesting the organ-protecting activity of lercanidipine and its capability to improve the elastic properties of the vascular wall.

Analysing the dynamics of biochemical parameters after 6-month therapy (**Table 5**) demonstrated a significant decrease in the concentration of creatinine by 7.3%, which was accompanied by a statistically significant increase in the GFR by 11% form the baseline level, and was indicative of improved filtration function of the kidneys. The patients from the subgroup with AH and chronic kidney diseases (CKD) also demonstrated significant improvement of the renal filtering function, which was confirmed by an increase in the GFR form 30.7±10.7 mL/min/1.73 m2 to 35.2±12.5 mL/min/1.73 m2 (p≤0.001) and a decrease in the creatinine concentration from 177.25±120.9 μmol/L to 161.9±118.1 μmol/L (p≤0.001).

By the end of the study, we revealed a statistically significant decrease in the index of generalised damage of the microvascular bed – the MAU level fell by 65.84% from the baseline value (p≤0.01).

As can be seen from **Table 5**, the carried out therapy was also accompanied by a decrease in TCH by 2.9% (95% CI 2.25-2.57) and LDL CH by 17% (95% CI 4.87-5.2). No significant alterations in the levels of blood glucose, uric acid and urea were observed, thereby strongly suggesting that lercanidipine may be regarded as a metabolically neutral antihypertensive agent.

At the end of the study, there was no statistically significant dynamics observed for the left ventricular myocardium mass index (LVMMI), thickness of the interventricular septum (IVS) and the left ventricular posterior wall (LVPW), most likely because of a short duration of the study.

DISCUSSION

All patients with a verified diagnosis of stage 2 – 3 AH in our study were prescribed to take lercanidipine as an antihypertensive agent. Lercanidipine is a third-generation calcium channel antagonist, being a derivative of 1,4-dihydropyridine, regulating activity of L-type channels through the S-enantiomer (5). Its main mechanism of action consists in inhibition of the transmembrane current of calcium ions, followed by the development of vasodilation of smooth muscle cells of vessels and improvement of regional blood circulation. The drug possesses very high lipophilicity, is capable of being slowly released from the lipid layer of cell membranes, owing to which fact it may accumulate in high concentrations in smooth muscle cells of vessels and render an ultra-long effect. Being highly vasoselective, in therapeutic doses, it exerts no negative inotropic effect, does not influence vascular permeability, extremely rarely induces oedemas of ankles, which was demonstrated in several large trials (LEAD, ELYPSE, COHORT) where lercanidipine reliably confirmed its high level of efficacy and tolerance as compared with other drugs of this class (6-9).

In our study, lercanidipine demonstrated high antihypertensive efficacy when administered both as monotherapy and in a combination with an ACE inhibitor. All patients with stage 2 and 3 AH in 100% of cases by the end of the study achieved the target level of AP. Treatment with lercanidipine was well tolerated by the patients, with no side effects observed.

In routine clinical practice, the ankle-brachial index (ABI) is used to determine reveal stenosing and occlusive diseases of lower-limb arteries, preclinical atherosclerotic lesions, increased rigidity of the vascular wall. A series of works studied and confirmed diagnostic and prognostic significance of the ABI as a marker of not only target-organ damage but also an independent predictor of an unfavourable prognosis in AH, increasing accuracy of determining the risk of cardiovascular complications (10-12).

Yet another sign of a diffuse asymptomatic lesion of peripheral vessels, reflecting elastic properties of major vessels, being simultaneously an index of subclinical damage of target organs and an independent risk factor for cardiovascular mortality in hypertensive patients is elevation of PP of more than 60 mm Hg (13-15). Thus, a cross-sectional study was aimed at determining interrelationship between the morphofunctional state of the main target organs in AH and the level of peripheral PP according to 24-hour BP monitoring and office blood pressure, revealing that in elderly and aged patients elevated PP is SAP-independent risk factor for hypertrophy and dilatation of the left ventricle of the heart. Average circadian PP was associated with increased aortic stiffness and atherosclerosis of lower-limb vessels. An elevated level of office PP was an independent predictor of an atherosclerotic lesion of the common carotid artery (16).

The findings of our study, with a high degree of significance demonstrated improved indices of the ABI and PP in hypertensive patients on the background of taking lercanidipine for 6 months, thus suggesting improved condition of the vascular wall, end-organ protection, and a decrease of the degree of risk factors for cardiovascular complications. Simultaneously, our study showed a highly statistically significant decrease in the level of atherogenic LDL cholesterol and TCH, which correlated with the data obtained on experimental models, demonstrating capability of lercanidipine to slow down the rates of the development of vascular atherosclerosis, irrespective of the level of AP and the level of LDL cholesterol (17). We cannot exclude the fact that owing to high vasoselectivity and lipophilicity lercanidipine may penetrate the lipid bilayer of membranes of atherosclerosis-altered vessels, which explains possibility of lercanidipine to prevent and slow down progression of vascular atherosclerosis.

Yet another preclinical sign of target-organ damage in AH is MAU, being pathological transcapillary loss of albumin, early manifestation of endothelial dysfunction characterized by a shift of vascular haemostasis towards vasoconstriction, being an early predictor of renal damage, a risk factor of the development and progression of AH and at the same time an independent unfavourable risk factor for cardiovascular, cerebrovascular complications and mortality (18-21). It was confirmed that MAU in hypertensive patients without insulin resistance or type 2 diabetes mellitus is a risk factor for the development of total nephroangiosclerosis (22).

The authors of the DIAL large double-blind randomized study evaluated the effect of lercanidipine on the albumin excretion rate in patients with type 2 diabetes mellitus, AH and persistent MAU. After 12 months of therapy they observed a significant reduction in MAU, correlating with the value of intraglomerular pressure (23). Highly vasoselective lercanidipine is known to reduce total peripheral vascular resistance, to improve renal blood flow, to control excessive

vasoconstriction, acting at the level of both afferent and efferent arterioles, thereby reducing intraglomerular pressure (24).

In our study we revealed a significant decrease of MAU and the level of creatinine, improvement of the kidneys' filtering ability was documented by an elevated GFR, which made it possible to draw a conclusion of a nephroprotecting action of lercanidipine. At the same time, the obtained findings demonstrated improvement of the renal filtering function and a decrease in the creatinine concentration in patients with CKD, thus confirming the capability of the drug besides nephroprotection to slow down and prevent the development of chronic renal failure and suggesting that it may hence be prescribed to patients with both diabetic and non-diabetic nephropathy, as well as with chronic renal insufficiency (25).

Based on the results of our study, the drug also demonstrated metabolic neutrality which widens the possibilities of using lercanidipine in patients with gout, dyslipidemia, diabetes mellitus and metabolic syndrome.

CONCLUSION

Hence, the most important tasks while managing hypertensive patients include but are not limited to appropriate examination in order to detect evidence of early target-organ damage, accurate assessment of the risk for cardiovascular complications, selection of highly efficient antihypertensive therapy with pleiotropic organ-protecting properties, a low rate of side effects and high adherence of patients to treatment.

Therapy with lercanidipine ensures high antihypertensive efficacy in patients with stage 2 – 3 AH, good tolerance, possesses pleiotropic organ-protective properties: improves the state of the vascular wall, decreases arterial stiffness, corrects endothelial dysfunction, prevents and reduces the rates of progression of vascular atherosclerosis, possesses a nephroprotective effect, prevents the development and slows down progression of CKD, and is metabolically neutral. Taken together, these organ-protective properties of lercanidipine favourably contribute to decreasing the risk for the development of cardiovascular catastrophes.

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