

Regression of Left Ventricular Mass in Hypertensive Patients Treated With Perindopril/Indapamide as a First-Line Combination

The REASON Echocardiography Study

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Background: Increase in left ventricular mass (LVM) may be linked to morbidity and mortality in hypertensive patients. Arterial stiffness, systolic blood pressure (BP), and pulse pressure (PP) seem to be the main determinants of LVM. The perindopril/indapamide combination normalizes systolic BP, PP, and arterial function to a greater extent than atenolol. The aim of this study was to compare the effects of perindopril (2 mg)/indapamide (0.625 mg) first-line combination with atenolol (50 mg) on LVM reduction in hypertensive patients.

Methods: Two hundred fourteen patients with essential hypertension participating in the PREterax in Regression of Arterial Stiffness in a ContrOLled Double-BliNd (REASON), randomized, double-blind, parallel-group study, underwent M-mode two-dimensional-guided echocardiography.

Results: Perindopril/indapamide and atenolol were both effective at brachial BP reduction during the 12-month period. The systolic BP reduction was significantly greater with perindopril/indapamide than with atenolol ($-21.2 \nu -15.3$ mm Hg), whereas the reduction in diastolic BP was similar

between treatment groups ($-12.1 \nu -11.3$ mm Hg). Reduction in LVM was higher with perindopril/indapamide than with atenolol. The between-group difference was significant for LVM ($-13.6 \nu -4.3$ g, $P = .027$), LVM/body surface area (LVMI_1 , $P = .032$), and LVM/body height^{2.7} (LVMI_2 , $P = .013$). The 124 patients with LV hypertrophy at baseline showed greatest LVM regression (LVM: $-22.5 \nu -8.9$ g, $P = .009$; LVMI_1 , $P = .031$; LVMI_2 , $P = .028$). The reduction in LVM adjusted for brachial systolic BP and heart rate was still significantly greater with perindopril/indapamide than with atenolol.

Conclusions: Treatment, based on a first-line perindopril/indapamide combination in hypertensive patients, was more effective than atenolol on regression of echocardiographic indices of LVM and LV hypertrophy. *Am J Hypertens* 2004;17:660–667 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, left ventricular hypertrophy, left ventricular mass, echocardiography, perindopril/indapamide combination.

It is well established that hypertension, defined as systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg,^{1–3} represents a major risk

factor for morbidity and mortality. Much emphasis has previously been placed on risk reduction associated with diastolic BP control. However, recent epidemiologic stud-

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ies as well as recommendations from hypertension guidelines have shown that the brachial systolic BP is a better guide for evaluating cardiovascular risk than brachial diastolic BP.^{2–5} Pulse pressure (PP) and arterial stiffness may also be independent cardiovascular risk factors.^{6–10}

Hypertensive patients with concurrent cardiovascular structural changes such as left ventricular hypertrophy (LVH) have a greater mortality risk than those with hypertension alone.^{11–14} There is evidence to suggest that a parallel cardiac and vascular adaptation exists in arterial hypertension¹⁵ with a positive relationship between cardiac mass and arterial stiffness.¹⁶ A direct relationship between cardiac mass and BP has been demonstrated, and the main pressure determinants of left ventricular mass (LVM) in essential hypertension are systolic BP and PP.^{7,17–23} Reduced aortic distensibility and compliance may participate in the genesis of cardiac hypertrophy in hypertension. Arterial compliance also determines the pulsatile amplitude of the pressure wave and its reduction induces a selective increase in systolic level and PP. Consequently a different response after antihypertensive treatment has been demonstrated in cardiac and arterial changes.^{24,25}

A first-line combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril (2 mg) and indapamide (0.625 mg), a sulphamoyl diuretic that belongs to the thiazide group, has been shown to have a favorable efficacy:safety ratio^{26,27} and superior antihypertensive efficacy in comparison with enalapril, losartan, and irbesartan.^{28–30} Recently, PREterax in Regression of Arterial Stiffness in a ContrOlled Double-BliNd Study (REASON) has shown that the perindopril/indapamide antihypertensive treatment normalized systolic BP, PP, and arterial function to a greater extent than atenolol in hypertensive patients.³¹ Moreover, the perindopril/indapamide combination has shown a beneficial effect on cardiac hypertrophy and capillary density in experimental hypertension.³² Given such findings it is timely to compare cardiac mass structural changes after perindopril/indapamide combination or atenolol in the treatment of hypertensive patients.

In this article we present the results from the REASON echocardiography ancillary study. This study investigated the long-term effects of perindopril/indapamide first-line combination compared with atenolol on echocardiographic indices of LVM in hypertensive patients.

Methods

Study Design

The REASON study was a 12-month, randomized, double-blind, parallel-group study conducted in 13 countries, which has previously been published.³¹ REASON compared the efficacy and safety of perindopril (2 mg)/indapamide (0.625 mg) or atenolol (50 mg) in the treatment of 471 patients with essential hypertension.

Men and women aged 18 to 84 years, with a diagnosis of uncomplicated essential hypertension (systolic BP

≥160 mm Hg and <210 mm Hg; diastolic BP ≥95 mm Hg and <110 mm Hg), were eligible for inclusion.

After a 4-week placebo wash-out period, patients were randomized to receive one capsule of perindopril (2 mg)/indapamide (0.625 mg) or atenolol (50 mg) once daily for 12 months. After 3 months of treatment and then at every 3-month period until the end of the study, the dose could be increased to two tablets per day if the systolic BP remained >160 mm Hg or the diastolic BP >90 mm Hg ($n = 103$ perindopril/indapamide and 92 for atenolol; log rank test $P =$ not significant [NS]). Other antihypertensive drugs were not allowed during the study follow-up. At study end, dosage was progressively decreased during 8 to 15 days to avoid any complications that might result from abrupt atenolol withdrawal. This study was performed in accordance with the Declaration of Helsinki, the protocol was approved by the Ethic Committees according to national regulations, and all patients provided written informed consent to participate.

Patients who participated in the echocardiography study ($n = 214$) had an echocardiogram recorded at baseline (month 0) and after 12 months of effective treatment (end value).

Efficacy Assessments

Left ventricular dimensions were assessed using two-dimensionally directed M-mode echocardiography. A quality control procedure was established for the validation of the echocardiographic evaluations. Each examination was recorded on S-VHS tape and readings of the measurements were performed centrally, on five cycles by two experienced physician readers blind to treatment, patients, and visit, and the values of both readers were then averaged.

Echocardiographic measurements (left ventricular internal dimension [LVID], posterior wall thickness [PWT], and interventricular septum thickness [IVST]) were assessed at the end of diastole, defined as the peak of the R wave of the QRS complex, and in accordance with the recommendations of the American Society of Echocardiography.³³ The intraobserver and interobserver reproducibility of the echocardiographic measurements was tested in a parallel series of 10 subjects with three replications, the methodology of which is described in detail elsewhere.^{34,35} The coefficient of variation was below 3%, the intraobserver correlation was $r = 0.99$ mm, and the interobserver correlation was $r = 0.96$ mm (mean difference, 0.05 ± 0.03 mm).

The LVM was calculated from the Penn convention according to the standard Devereux formula³⁶: $LVM (g) = 1.04 [(IVSTd + PWTd + LVIDd)^3 - LVIDd^3] - 13.6$, and converted into LVM index (LVM_1) by dividing by body surface area. Due to a possible overcalculation in overweight patients, LVM divided by body height^{2,7} was also calculated (LVM_2).³⁷

Brachial systolic BP, diastolic BP, and heart rate were determined after a 10-min rest in the supine position using

Table 1. Baseline characteristics for patients included in the study

	All Patients (n = 214)		Left Ventricular Hypertrophy Patients (n = 124)	
	Per/Ind (n = 110)	Atenolol (n = 104)	Per/Ind (n = 70)	Atenolol (n = 54)
Sex (M:W) (%)	61:39	68:32	57:43	63:37
Age (y)	53.2 (11.8)	53.7 (11.4)	54.3 (11.5)	51.8 (12.1)
BMI (kg/m ²)	26.7 (2.8)	26.8 (2.9)	26.8 (3.0)	26.9 (2.7)
Systolic BP (mm Hg)	162.1 (13.7)	161.5 (16.2)	162.0 (13.6)	162.7 (15.6)
Diastolic BP (mm Hg)	99.0 (7.0)	99.3 (7.3)	98.8 (7.0)	100.0 (7.8)
Mean BP (mm Hg)	120.0 (6.7)	120.0 (7.9)	119.9 (6.3)	120.9 (7.9)
Pulse pressure (mm Hg)	63.1 (15.0)	62.2 (16.5)	63.2 (15.5)	62.8 (16.4)
Heart rate (beats/min)	72.7 (10.4)	71.8 (7.9)	72.8 (11.0)	71.1 (7.1)

BMI = body mass index; BP = blood pressure; Per/Ind = perindopril/indapamide combination. Mean (SD) values presented unless otherwise stated.

a mercury sphygmomanometer and stethoscope. Brachial PP was calculated from individuals' values of systolic BP and diastolic BP.

Tolerability Assessments

Any adverse events were recorded at clinic visits. Variations in laboratory parameters were measured between baseline and end values. Tolerability data are presented for the entire REASON study population.

Statistical Analyses

All analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC). Quantitative variables are presented as mean changes (with standard deviation) from baseline to end value, unless otherwise stated. Patients who received at least one dose of treatment were included in an intent-to-treat analysis. A last observation carried forward approach was used if data were missing. Patients with LVH at baseline (LVMI₁ >100 g/m² for women and >120 g/m² for men) were included in a per-protocol subgroup analysis prespecified in the protocol.

Within-group effect was assessed using a two-tailed Student *t* test for paired samples. Between-group comparisons were assessed on the change at last evaluation using a covariance analysis, which included the treatment group as a factor, and age, sex, and the baseline value of the variable as covariates. A 5% threshold was considered significant. The relationship between LVM parameters and influence parameters was investigated using a stepwise linear regression procedure.

Results

Patient Characteristics

A total of 214 randomized patients, including 124 patients with LVH, were recruited to the echocardiography study. The baseline characteristics (Table 1) were similar in the two treatment groups and did not differ from those of the

entire population.³¹ Seventy-eight percent of patients completed 12 months of treatment. Forty-eight patients withdrew, 21 in the perindopril/indapamide group and 27 in the atenolol group because of adverse events (10 v 11, respectively), lack of efficacy (4 v 11), major protocol violations (1 v 2), and nonmedical reasons (6 v 3). Overall, the mean exposure to study drug was 312.3 days.

Brachial BP Assessment

Perindopril/indapamide and atenolol were both effective at BP reduction during the 12-month period. However, reduction in systolic BP was significantly greater with perindopril/indapamide than with atenolol (−21.2 v −15.3 mm Hg, respectively; *P* < .01). Significant reductions in diastolic BP were achieved in both treatment groups, but with no significant between-group differences (−12.1 v −11.3 mm Hg). The PP reduction was significantly greater for the perindopril/indapamide group than for the atenolol group (−9.1 v −4.0 mm Hg; *P* < .01). As expected, heart rate was lowered to a significantly greater extent with atenolol than perindopril/indapamide (−6.7 v −2.5 beats/min; *P* < .001; Table 2).

Echocardiographic Assessments

Left ventricular diameter, thickness, and mass did not differ between the two treatment groups at baseline (Table 3). At the end of the treatment period LVID, PWT, and IVST were all significantly reduced in the perindopril/indapamide group. There was no significant difference with atenolol (LVID: −0.62 v −0.02 mm; PWT: −0.29 v −0.10 mm; IVST: −0.22 v −0.12 mm, respectively; Table 3).

Consequently, LVM was considerably more reduced with the perindopril/indapamide than with atenolol. The between-group difference was significant, irrespective of whether this indice was expressed as LVM (−13.6 v −4.3 g; *P* < .05), LVMI₁ (−6.6 v −2.1 g/m²; *P* < .05), or LVMI₂ (−3.3 v −0.9 g/m^{2.7}; *P* < .05, respectively).

Table 2. Blood pressure (BP) changes, comparison between the two treatments

	All Patients (n = 214)		Left Ventricular Hypertrophy Patients (n = 124)	
	Per/Ind (n = 110)	Atenolol (n = 104)	Per/Ind (n = 70)	Atenolol (n = 54)
Systolic BP (mm Hg)				
Baseline	162.1 (13.7)	161.5 (16.2)	162.0 (13.6)	162.7 (15.6)
End value	140.8 (15.2)	146.2 (22.3)	139.3 (13.9)	145.1 (20.7)
Change	-21.2 (14.9)§	-15.3 (18.2)§	-22.7 (14.0)§	-17.6 (18.4)§
Difference* (SE)		-5.7 (2.2)‡		-5.4 (2.7)†
Diastolic BP (mm Hg)				
Baseline	99.0 (7.0)	99.3 (7.3)	98.8 (6.8)	10.0 (7.8)
End value	86.9 (9.0)	88.0 (11.0)	85.8 (8.6)	87.8 (10.8)
Change	-12.1 (8.9)§	-11.3 (9.9)§	-13.0 (6.9)§	-12.2 (9.8)§
Difference* (SE)		-0.9 (1.2) ^{ns}		-1.1 (1.5) ^{ns}
Pulse pressure (mm Hg)				
Baseline	63.1 (15.0)	62.2 (16.5)	63.2 (15.5)	62.8 (16.4)
End value	53.9 (13.1)	58.2 (17.0)	53.5 (12.4)	57.4 (16.7)
Change	-9.1 (11.5)§	-4.0 (14.6)‡	-9.7 (11.1)§	-5.4 (16.4)†
Difference* (SE)		-5.1 (1.8)‡		-4.3 (2.5) ^{ns}

Abbreviations as in Table 1.

* Adjusted for baseline; † $P < .05$; ‡ $P < .01$; § $P < .001$; ns = not significant [versus baseline for change values and between groups for difference values].

Mean (SD) values presented unless otherwise stated.

Patients with LVH at baseline demonstrated an even greater regression in LVM (LVM: $-22.5 \nu -8.9$ g; $\text{LVMI}_1 -11.3 \nu -5.3$ g/m², respectively; Table 4, Fig. 1).

The relationship between LV mass reduction and influence parameters was investigated using a stepwise linear regression procedure. Last step with systolic BP and heart rate for covariates showed that between treatment groups difference in adjusted mean LVM reduction was still significant (LVM -8.7 , $P = .034$). Systolic BP variation estimate was 0.23 and the statistical significance was bor-

derline ($P = .060$). Heart rate variation was not significant (estimate 0.02, $P = .92$).

Tolerability

Tolerability was assessed for the entire REASON population ($n = 471$). Both treatments were well tolerated and no differences in the incidence of side effects were reported. The most frequently reported adverse events (all occurring at $\leq 5\%$) were headache, dizziness, asthenia, and cough.³¹

Table 3. Changes in left ventricular morphology from baseline to end value

	All Patients (n = 214)		Left Ventricular Hypertrophy Patients (n = 124)	
	Per/Ind (n = 110)	Atenolol (n = 104)	Per/Ind (n = 70)	Atenolol (n = 54)
LVID (mm)				
Baseline	49.98 (3.79)	50.72 (4.54)	50.56 (3.29)	51.72 (3.84)
End	49.36 (3.86)	50.70 (4.11)	49.68 (3.29)	51.56 (3.98)
Change	-0.62 (1.97)†	-0.02 (2.71) ^{ns}	-0.88 (2.06)‡	-0.17 (1.87) ^{ns}
PWT (mm)				
Baseline	10.04 (1.12)	9.83 (1.04)	10.46 (1.01)	10.24 (0.95)
End	9.75 (1.03)	9.73 (0.96)	9.91 (1.02)	10.00 (0.86)
Change	-0.29 (0.79)‡	-0.10 (0.62) ^{ns}	-0.55 (0.76)‡	-0.24 (0.70)*
IVST (mm)				
Baseline	11.57 (1.70)	11.18 (1.35)	12.04 (1.70)	11.57 (1.31)
End	11.35 (1.60)	11.06 (1.37)	11.68 (1.69)	11.36 (1.29)
Change	-0.22 (0.76)†	-0.12 (0.84) ^{ns}	-0.36 (0.79)‡	-0.21 (0.79) ^{ns}

IVST = interventricular septal thickness; LVID = left ventricular internal dimension; PWT = posterior wall thickness; other abbreviations as in Table 1.

* $P < .05$; † $P < .01$; ‡ $P < .001$; ns = not significant [versus baseline for change values].

Mean (SD) values presented.

Table 4. Left ventricular mass indices changes, comparison between the two treatments

	All Patients (n = 214)		Left Ventricular Hypertrophy Patients (n = 124)	
	Per/Ind (n = 110)	Atenolol (n = 104)	Per/Ind (n = 70)	Atenolol (n = 54)
LVM (g)				
Baseline	241.68 (58.07)	238.01 (55.84)	259.77 (51.33)	258.20 (49.64)
End value	228.09 (51.67)	233.66 (51.90)	237.26 (45.16)	249.28 (47.06)
Change	-13.58 (28.88)§	-4.34 (28.05) ^{ns}	-22.51 (28.06)§	-8.92 (26.83)†
Difference* (SE)		-7.88 (3.55)†		-11.95 (4.49)‡
LVMI ₁ (g/m ²)				
Baseline	128.22 (26.58)	126.52 (25.20)	138.39 (21.71)	137.45 (21.60)
End value	121.61 (23.82)	124.48 (22.95)	127.10 (19.91)	132.13 (21.34)
Change	-6.61 (15.64)§	-2.05 (14.47) ^{ns}	-11.29 (15.43)§	-5.32 (15.06)*
Difference* (SE)		-4.03 (1.86)†		-5.58 (2.55)‡
LVMI ₂ (g/m ^{2.7})				
Baseline	58.10 (12.76)	57.31 (12.27)	63.10 (11.31)	62.54 (11.17)
End value	54.83 (11.31)	56.40 (11.75)	57.67 (10.25)	60.45 (11.09)
Change	-3.27 (6.98)§	-0.92 (7.21) ^{ns}	-5.43 (6.76)§	-2.09 (6.79)†
Difference* (SE)		-2.22 (0.89)†		-3.14 (1.15)‡

LVM = left ventricular mass; LVMI₁ = left ventricular mass/body surface area; LVMI₂ = left ventricular mass/height^{2.7}; other abbreviations as in Table 1.

* Adjusted for age, sex, and baseline.

Within group comparisons for change value and between group comparisons for difference value: † $P < .05$; ‡ $P < .01$; § $P < .001$; ns = not significant.

Mean (SD) values presented unless otherwise stated

In the echocardiography study, withdrawal rate due to adverse events was similar between atenolol and perindopril/indapamide (11 v 10, respectively).

Discussion

In this REASON echocardiography study, the first-line combination perindopril/indapamide was superior to atenolol in regression of echocardiographic indices of LVM, as shown by the significant reductions in LVM, LVM/body surface area, and LVM/body height^{2.7}. These benefits were more pronounced in patients who had LVH at entry. Reduction in systolic BP was significantly greater with perindopril/indapamide than with atenolol, whereas the reductions in diastolic BP were similar between treatment groups. The results are robust as the study design complies with criteria for informative trials on LVH regression,³⁸ namely, sufficient number of subject (214), representative population, long study duration (12 months), double-blind randomization, and blinded echocardiographic readings. On average, atenolol decreased heart rate significantly more than the combination of perindopril/indapamide. Nevertheless, the distribution of the individual heart rates was great and the intersection between the values under atenolol and the values without atenolol was large. The blindness to treatment, patient, and visits could be considered as sufficient to avoid a strong probability that the reader could guess from which treatment group a tracing came. Antihypertensive drugs other than the randomized treatments were not allowed during the study and the comparison between the treatment

groups reflects only the difference between treatment with the perindopril/indapamide combination and treatment with atenolol.

These results are consistent with previous studies suggesting that some antihypertensive drugs may reverse LVM more effectively than others. A meta-analysis³⁹ shows that after correction for BP, LVM regression is more evident with ACE inhibitors than with other antihypertensive agents. The Losartan LVH Regression (REGAAL) study⁴⁰ compared treatment with either an angiotensin II antagonist (losartan) or atenolol in 225 hypertensive patients with LVH during a 36-week period. The reduction in LVMI was -4.5 g/m² with atenolol and -7.4 g/m² with losartan. In our study the reduction in LVMI with atenolol was similar (-5.3 g/m²) taking into account the longer study duration (48 weeks).

The larger reduction after treatment with perindopril/indapamide (-11.3 g/m²) could be due to the specific effect of this combination. A direct beneficial effect of treatment on myocyte hypertrophy, myocardial fibrosis periarterolar, total interstitial collagen, structural and functional coronary microcirculation, or vascular thickness are possible explanations.^{32,41-43}

The greater effect of perindopril/indapamide on brachial systolic BP could explain its superior effect on LVM reduction, as the main pressure determinants of LVM are systolic BP and PP.²¹⁻²³ Moreover, the lowering heart rate effect of atenolol might also modify LVM.⁴⁴ Nevertheless, to assess the effect on LVM beyond the peripheral hemodynamic changes, the tests were adjusted for brachial

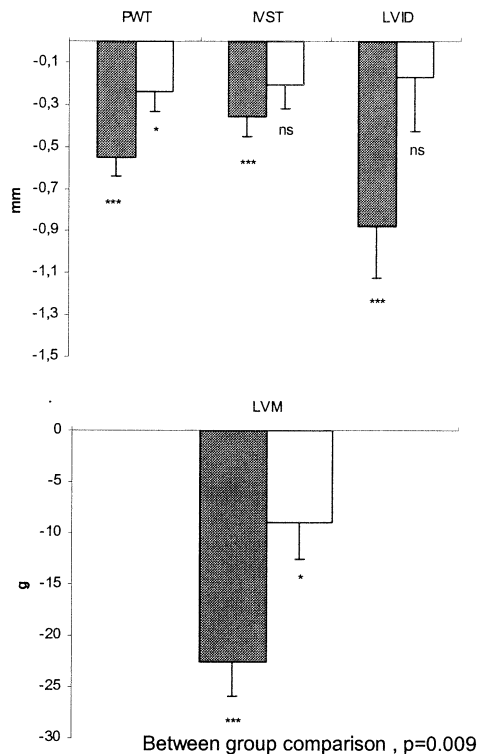


FIG. 1. Change from baseline to end value for left ventricular internal dimension (LVID), posterior wall thickness (PWT), interventricular septum thickness (IVST) and left ventricular mass (LVM) for patients with left ventricular hypertrophy ($n = 124$). Mean \pm SE. Shaded bars = perindopril/indapamide combination; open bars = atenolol. * $P < .05$; *** $P < .001$; ns = not significant.

systolic BP and heart rate variation without altering the difference (-8.7 mm; $P < .05$), which can, therefore, be considered to reflect differences in the two drugs that are independent of their ability to lower brachial systolic BP or heart rate.

The main REASON results^{31,45} demonstrated that perindopril/indapamide reduced central (carotid) and peripheral (brachial) systolic BP and PP to a significantly greater extent than atenolol, and that these benefits were more pronounced for central systolic BP and PP. Perindopril/indapamide attenuated carotid wave reflections to a greater extent than atenolol, which accounted for the beneficial effects on central systolic BP and PP. Given that LVM is affected more by central rather than peripheral hemodynamic changes, the more pronounced effects of perindopril/indapamide on central systolic BP and PP lowering could explain its greater effect on LVM reduction. It has already been demonstrated that aortic impedance^{15,16} and PP amplification^{7,17–19,21–23} are involved in cardiovascular factors influencing LVM, and that the effects of antihypertensive agents on these parameters may differ according to the drug involved.⁴⁶

It will be interesting to determine whether the specific effect of the perindopril/indapamide combination on LVM regression will result in morbidity and mortality reduction over that observed with adequate BP control. The effect of

the perindopril/indapamide combination on morbidity and mortality is the subject of an ongoing double-blind controlled study in more than 10,000 subjects,⁴⁹ the main results of which are expected in 2006. The study of LVM in the Hypertensive Subject (MAVI)⁴⁷ showed that elevated LVM is a cardiovascular disease risk independently of brachial systolic BP. In the Losartan Intervention for Endpoint Reduction (LIFE) study, after adjustment for treatment and other factors, regression of LVH was found to be associated with an improved prognosis independently of brachial BP.⁴⁸

In conclusion, the findings have shown that the first-line combination perindopril (2 mg)/indapamide (0.625 mg) was more effective than atenolol in systolic BP and PP reduction and improvement of LVM parameters, during a 12-month treatment period. Perindopril/indapamide may be a valuable treatment choice, with a view to reducing the long-term morbidity and mortality risks associated with hypertension or LVH.

Appendix

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