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## Efficacy and Tolerability of Losartan in Patients with Essential Hypertension: a Multicentre, Double-Blind Comparison of Losartan with Metoprolol

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*A multicentre, randomised, double-blind, comparative study of antihypertensive efficacy and safety of losartan and metoprolol was carried out in 77 patients with mild to moderate essential hypertension. Normalisation of sitting diastolic blood pressure (siDBP) and sitting systolic blood pressure (siSBP) at the end of the study was considered as the primary criterion for evaluation. A decrease of siDBP for at least 10 % and that of siSBP for at least 15 % was considered as response to treatment. After 2 weeks of single placebo run-in period the patients were randomised to either losartan 50 to 100 mg od or metoprolol 50 to 100 mg bid. After 3 weeks of the treatment the initial dose of both drugs was doubled if target siDBP was not achieved. After 6 weeks of monotherapy hydrochlorothiazide 12.5 mg was added for the last 3 weeks if necessary.*

*Losartan and metoprolol significantly reduced siSBP and siDBP versus baseline:  $-20.8/15.9$  mmHg and  $-16.2/16.6$  mmHg, respectively (all  $p < 0.001$ ). There was no significant difference between the treatment regimens found during the study in regard to siSBP and siDBP decrease. In the losartan arm the primary criterion for efficacy was achieved in 72.3 % for both siSBP and siDBP. In patients treated with metoprolol these results were 63.0 and 85.2 %, respectively (n.s.). No significant differences between treatment regimens were observed in regard to complete normalisation of blood pressure ( $< 140/90$  mmHg in single patient) and overall blood pressure response. In both groups heart rate decreased significantly and similarly. Both treatments were well tolerated. Adverse events were reported by 16.3 % of patients treated with losartan and 21.4 % of patients treated with metoprolol (n.s.). There were no serious adverse events.*

*Conclusion: In this study in patients with mild to moderate essential hypertension, losartan in comparison with metoprolol exerted substantial and comparable antihypertensive efficacy, as well as a similar safety profile. J Clin Basic Cardiol 2005; 8: 43–6.*

**Key words:** essential hypertension, losartan, metoprolol.

Arterial hypertension is widely recognised as the most common cardiovascular disease in countries with western life-style. Hypertension is a potent risk factor for all major cardiovascular events, but the most for cerebrovascular accidents particularly in the elderly [1]. Cardiovascular morbidity and mortality may be reduced by the control of blood pressure but the extent of reduction depends on the magnitude of blood pressure lowering [2]. Blood pressure reduction achieved with beta-blockers and diuretics was the best-recorded intervention to date for prevention of cardiovascular morbidity and death in patients with hypertension. A significant reduction of the incidence of stroke (38 %), coronary artery disease (16 %), and cardiovascular mortality (21 %) was achieved with blood pressure lowering of average 9–10/5–6 mmHg over 5 years by use of diuretics and beta-blockers [3]. Later, comparable but not better results were obtained in trials with calcium antagonists and/or angiotensin-converting enzyme (ACE) inhibitors [2, 4–8].

In numerous comparative studies the recently introduced class of antihypertensive agents, angiotensin II receptor antagonists, has proven a comparable antihypertensive efficacy with other classes of antihypertensive drugs but much better safety profile. Until now, in patients with high risk only losartan demonstrated better efficacy in reducing the composite cardiovascular endpoints and stroke [9]. So, LIFE study was the first comparative trial in which a newer antihypertensive drug exerted significantly better protection against overall cardiovascular morbidity and stroke than an older drug [9]. Earlier some studies with losartan [10, 11],

valsartan [12], and irbesartan [13, 14] already suggested that in this respect angiotensin II receptor antagonists will not differ from proven drug classes. In hypertension, they have been compared more often with atenolol than with other beta-blockers. Angiotensin II receptor antagonists exerted similar antihypertensive efficacy but the incidence of adverse events was much lower than with atenolol [15–19].

The aim of this study was first to prove the antihypertensive efficacy of losartan in a double-blind study, and secondly, to compare the efficacy and safety of losartan with the cardioselective beta-blocker metoprolol that has not been extensively compared with angiotensin II receptor antagonists in patients with non-complicated mild to moderate essential hypertension.

### Methods

It was a multicentre, prospective, randomised, double-blind, parallel-group, clinical study, carried out at four medical centres in the Czech Republic (one), Poland (one), and Slovenia (two). 77 outpatients, male and female in the age of 18 to 75 years with essential hypertension were eligible. The main inclusion criteria were a sitting diastolic blood pressure (siDBP) of 95–114 mmHg and a sitting systolic blood pressure (siSBP)  $< 180$  mmHg. The patients had to be angiotensin II receptor antagonist- or beta-blocker-naive. In patients who were already treated with other antihypertensive drugs in monotherapy, the control of blood pressure had to be under satisfactory. These drugs were withdrawn at the in-

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clusion. By decision of the National Ethics Committee in Slovene centres only untreated patients at the time of inclusion were allowed to enter the study. Common exclusion criteria were in force for this study, among them women in childbearing period, secondary hypertension, malignant hypertension, bradycardia < 50 beats/min<sup>-1</sup>, all stages of atrioventricular block, stroke or transient cerebral ischaemia within the last 12 months, myocardial infarction within the last 6 months, heart failure, angina pectoris, diabetes mellitus (with the exception of stable type 2 controlled with peroral agents) etc.

The study was approved by local ethics committees and authorities. The patients had to sign the written informed consent prior to inclusion.

All patients underwent basic cardiological examination, including routine ECG and laboratory examinations. At the visits after 3 and 6 weeks of active treatment serum concentration of creatinine and potassium and proteinuria were determined. At the final visit all examinations performed at the inclusion were repeated.

All patients underwent the controlled single-placebo run-in (wash-out) period of 14 days of duration. Patients were excluded from the study in the case of blood pressure ≥ 180 and/or ≥ 115 mmHg at any time during run-in period. After the placebo phase the eligible patients were randomised to either losartan (group A) or metoprolol (group B). Randomisation ratio losartan : metoprolol was 2 : 1. The initial dose of losartan was 50 mg once daily and that of metoprolol 50 mg twice daily. At the visit after 3 weeks of double-blind treatment with lower dose of both drugs, the patients in whom siDBP achieved normal values (< 90 mmHg) continued the initial treatment. In other patients the doses were doubled for the next 3 weeks. Then, the properly controlled patients (siDBP < 90 mmHg) continued to take initial or doubled doses. To the patients in whom siDBP exceeded 89 mmHg hydrochlorothiazide (HCTZ) 12.5 mg once daily was added for the last 3 weeks.

Blood pressure was measured according to the recommendations of the American Heart Association using mercury sphygmomanometer. After 15 minutes of rest 3 consecutive measurements were taken at 2-minute intervals. The average of the second and third measurement was then calculated and registered.

The aim of the treatment during this study was to reduce the siDBP < 90 mmHg and siSBP < 140 mmHg. Primary criterion of efficacy was the value of blood pressure at the end of the study. The final evaluation of efficacy was made by the investigators using the following criteria: normalisation of blood pressure (< 140/90 mmHg), response i. e. reduction of siDBP by at least 10 % and siSBP by at least 15 % but without normalisation, and no response i. e. reduction of siDBP by less than 10 % and siSBP by less than 15 %.

The study was conducted between September 2000 and May 2001.

**Table 1.** Demographic characteristics of each treatment group

Mean values	Group	
	A (n = 49)	B (n = 28)
Age (years)	50.6	54.3
Height (cm)	172.4	170.5
Weight (kg)	81.9	82.8
BMI* (kg/m <sup>2</sup> )	27.5	28.5

\* Body Mass Index

A personal computer with SAS software was used for double data entry, data management, and statistical analysis. The quantitative variables are described by their mean and standard deviation values. For the quantitative variables the Student's t-test taking into account the possible inequality of the variance and Wilcoxon rank test were performed. The comparison between the two groups for the qualitative variables was done by Chi square test and Cochran-Mantel-Haenszel test. Analysis of efficacy was per protocol. Safety analysis included all patients from the time of randomisation to the end of the study, or to the point at which the study drug was permanently stopped, whichever came first.

## Results

### Study Sample

A total of 77 patients were enrolled. 74 patients completed the study according to the protocol. Three patients left the study prematurely. Two of them, who discontinued the study after few days of active treatment were excluded from the statistical analysis. The data of one patient who left the study after 6 weeks of active treatment were included into analysis up to the time of withdrawal.

49 patients, 29 males and 20 females were randomised into group A (losartan), and 28 patients, 14 males and 14 females into group B (metoprolol). Baseline characteristics of both groups are shown in Table 1.

31 patients (63 %) in group A and 17 patients (61 %) in group B reported no symptoms attributable to hypertension at inclusion. Ninety-two percent of patients in both groups took no other medication. Four patients (8 %) in group A and 2 patients (7 %) in group B were treated for other clinical conditions (dyslipidaemia, hyperuricaemia, viral infection).

Two patients in group A and one patient in group B interrupted the treatment due to adverse events: one patient in group A left the study owing to bradycardia, another owing to chest pain, while one patient in group B left the study owing to symptomatic hypotension. They are not included for statistical analysis.

### Blood Pressure and Heart Rate

The changes in siSBP and siDBP are presented in Table 2. Both treatment regimens significantly reduced siSBP, siDBP, and heart rate at the end of the study when compared with baseline. Statistically significant blood pressure reduction was observed already at week 3, i. e. after the initial dose of both drugs. There was no significant difference in blood pressure or heart rate between two treatment regimens found during the study: week 0: p < 0.85, week 3: p < 0.12, week 6: p < 0.21, week 9: p < 0.28.

**Table 2.** Mean changes in siSBP and siDBP during the study (mmHg)

	Group	
	A	B
Baseline siSBP* (mmHg)	153.7	150.8
after 3 weeks (mmHg)	-14.6 <sup>‡</sup>	-12.5 <sup>‡</sup>
after 6 weeks (mmHg)	-17.0 <sup>‡</sup>	-16.0 <sup>‡</sup>
after 9 weeks (mmHg)	-20.9 <sup>‡</sup>	-16.8 <sup>‡</sup>
Baseline siDBP <sup>†</sup> (mmHg)	100.3	99.3
after 3 weeks (mmHg)	-10.6 <sup>‡</sup>	-11.1 <sup>‡</sup>
after 6 weeks (mmHg)	-14.0 <sup>‡</sup>	-15.8 <sup>‡</sup>
after 9 weeks (mmHg)	-15.7 <sup>‡</sup>	-16.7 <sup>‡</sup>

\*sitting systolic blood pressure, <sup>†</sup>sitting diastolic blood pressure, <sup>‡</sup>p < 0.001

In 24 patients (50 %) in group A and in 10 patients (37 %) in group B the initial doses had to be doubled at week 3 (n.s.). A diuretic had to be added in 12 patients (25 %) in group A and in 5 patients (15 %) in group B at week 6 (n.s.).

At the end of the study the assessment of treatment efficacy was classified according to predefined classification (see above). No statistically significant differences could be established between two treatment regimens. This assessment is presented in Table 3.

The satisfactory blood pressure decrease (normalisation plus response) was achieved in 36 patients (76.6 %) treated with losartan (plus diuretic) compared with 22 patients (81.5 %) treated with metoprolol (plus diuretic). Target siDBP (< 90 mmHg) was achieved in 34 patients (72.3 %) in group A and in 23 patients (85.2 %) in group B. Target siSBP (< 140 mmHg) was achieved in 34 patients (72.3 %) in group A and in 17 patients (63.0 %) in group B. The complete normalisation of blood pressure (SBP and DBP < 140/90 mmHg) was observed in 55.3 % of patients treated with losartan (plus diuretic) compared with 66.7 % of those receiving metoprolol (plus diuretic) (n.s.).

#### Adverse Events

On the whole, 14 patients (18.2 %) [8 patients (16.3 %) in group A and 6 patients (21.4 %) in group B] reported at least one adverse event during the study (n.s.). The most frequent adverse events were vertigo (4 patients), headache (3 patients), dizziness (2 patients), and palpitations (2 patients). In 3 patients the treatment was interrupted owing to adverse events (see above). No serious adverse events were noted. Regarding absolute and/or cut off values no clinically important changes in laboratory parameters were observed.

### Discussion

For many years the treatment of hypertension has been hampered by frequent and untoward side effects of antihypertensive medication. For years the medical community has called for new agents that would be effective given once a day and, perhaps more importantly, exhibit no side effects. Over the last 20 years we have come closer achieving this goal; cases in point are the ACE inhibitors and long acting calcium antagonists. With the development of the new class of angiotensin II receptor antagonists, and their high affinity for the AT-1 receptor subtype, we have come much closer to the realisation of this goal. This pharmacological group has been already appointed as the first choice by recent WHO/ISH guidelines, but the official indication has remained side effects with other drug classes, for example cough provoked by ACE inhibitors [20, 21]. Data comparing endpoints like renal protection in patients with type 2 diabetes mellitus [11, 13, 14] and data on reduction of the composite endpoint of cardiovascular death, myocardial infarction, and stroke in hypertensive patients with high risk were published recently [9]. The American Diabetes Association recently recommended angiotensin II receptor antagonists as the first choice

for the treatment of hypertension in diabetes type 2 with microalbuminuria or clinical nephropathy [22].

We have compared the efficacy and safety of the first representative angiotensin II receptor antagonists losartan with in Europe widely used beta-blocker metoprolol in a double-blind, multicentre study. The first aim of the study, the antihypertensive efficacy of losartan, was undoubtedly confirmed. For incipient monotherapy and final combination with low-dose diuretic 55 % successfully treated patients (normalisation of blood pressure) and 77 % overall response to treatment was comparable with response to therapy with losartan or other antihypertensive agents from this group achieved in previous studies [23, 24].

The comparison with metoprolol seems to be more interesting although this was only the second aim of the study. Namely, the design of the study with the randomisation ratio 2 : 1 in favour of losartan was originally not arranged to comparison. Therefore, the comparison can not be fully reliable. The assessment of the efficacy of losartan and metoprolol does not bring any surprise. Both drugs exerted similar antihypertensive efficacy. Nevertheless, with respect to normalisation of blood pressure (< 140/90 mmHg), metoprolol proved to be non-significantly more efficacious than losartan (66.7 % vs. 55.3 %, respectively). But the overall response to therapy was found to be nearly equal in both treatment regimens: 76.6 % in the losartan group and 81.5 % in the metoprolol group. Both drugs exerted greater effect on diastolic blood pressure than on systolic one. It appeared to be true particularly for metoprolol. The patients receiving metoprolol were on average nearly 4 years older than those receiving losartan. Perhaps the reason for greater resistance of systolic blood pressure in the metoprolol group has to be looked for in the age difference. Since the absolute blood pressure reduction was a little bit higher in the losartan group, the lower normalisation rate and higher upward titration rate could be explained by somewhat higher blood pressure in losartan group at baseline.

The greatest mean changes of diastolic and systolic blood pressure were observed in patients treated with initial doses of both drugs throughout the entire study. This may mean that the patients in whom the dose titration was needed, suffered from more serious disease. But, even the addition of diuretic to doubled doses did not increase essentially the effect, with the exception of systolic blood pressure in patients treated with metoprolol. One would expect that the addition of diuretic will increase the antihypertensive effect of both losartan and metoprolol. However, the adding of a low dose of HCTZ resulted in a rather small decrease of blood pressure, but only a small number of patients was treated with combination therapy (12 vs. 6) in the last period of the study, so it is not possible to draw any final conclusion from these results. Both combinations (diuretic with beta-blocker or angiotensin II receptor antagonist) are recommended by official guidelines [20, 25, 26].

The only comparative study of losartan *versus* metoprolol was performed in Finland, but the primary purpose of this study was the effectiveness on insulin sensitivity in hypertensive patients [27]. After 12 weeks of double-blind, placebo-controlled monotherapy with losartan 50 mg once daily or metoprolol 95 mg once daily the blood pressure decreased by 13/6 mmHg in patients treated with losartan and by 4/8 mmHg in the metoprolol group. Both drugs did not have any significant adverse effects on insulin secretion, glucose tolerance, or lipids and lipoproteins. However, this study is not comparable to the presented one as it had different purpose and design.

**Table 3.** Assessment of treatment efficacy

Group	Normalisation of BP* (n.s.) <sup>†</sup>		Satisfactory BP* decrease (n.s.) <sup>†</sup>		No response (n.s.) <sup>†</sup>	
	n	%	n	%	n	%
A	26	55.3	36	76.6	11	23.4
B	18	66.7	22	81.5	5	18.5

\*blood pressure, <sup>†</sup>no significance

In the 12 week-study of Dahlöf and co-authors the monotherapies with losartan 50–100 mg and atenolol 50–100 mg were compared [16]. In antihypertensive treatment, the daily dosage 50–100 mg of atenolol is thought to be equivalent to 100–200 mg of metoprolol. In this study no difference was found in the antihypertensive efficacy of both treatment regimens. The absolute reduction of blood pressure after 6 weeks in the presented study (losartan *vs.* metoprolol), when all patients were treated with monotherapy, was greater in both groups than in the losartan *vs.* atenolol study after 12 weeks: –17.2/14.2 mmHg (losartan) and 15.4/15.7 mmHg (metoprolol) compared with –12.2/8.3 mmHg (losartan) and 11.3/10.1 mmHg (atenolol).

In a trial with patients with isolated systolic hypertension these were treated for 8 weeks with the lower dose of losartan or atenolol, 50 mg once daily of each [17]. Then HCTZ 12.5 mg was added in patients in whom systolic blood pressure remained  $\geq 160$  mmHg. In patients not titrated to HCTZ the mean systolic blood pressure reduction was 25.0 mmHg in the losartan group and 25.4 mmHg in the atenolol group. This effects seem to be greater than in our study but the studies are not fully comparable due to different inclusion criteria.

Usually, the dose of irbesartan 150–300 mg appears to be equivalent to 50–100 mg of losartan in the treatment of hypertension [18]. In a study of 24 weeks of duration [19] the normalisation of diastolic blood pressure was achieved in 72 % of patients treated with 75–150 mg of irbesartan daily and in 63 % of patients receiving atenolol 50–100 mg daily (n.s.). In another study of 48 weeks of duration systolic and diastolic blood pressure reductions were similar with 150 mg of irbesartan and with 50 mg of atenolol daily [18]. But the effect of irbesartan on left ventricular mass was significantly greater: a decrease of 47 % *vs.* 32 % [28]. In the LIFE study losartan lead to a significantly greater decrease of ECG-left ventricular hypertrophy than atenolol [9].

So, the antihypertensive efficacy of angiotensin II receptor antagonists appears not to be significantly different from that of beta-blockers, but the difference in favour of former treatments seems to exist in organ protection.

Knowing data arising from clinical studies with angiotensin II receptor antagonists in whom the placebo-like incidence of adverse events was reported, a low incidence of adverse events in patients treated with losartan in our study has been expected. No typical clinically significant adverse events were observed after metoprolol in our study and metoprolol demonstrated a similar safety profile than losartan. In other controlled clinical trials, losartan was better tolerated than other antihypertensive drugs as determined by the incidence of patients reporting any drug-related adverse experience [19]. The percentage of any drug-related adverse event in patients treated with losartan was 15.3 compared with 26.5 in patients treated with atenolol, that was similar to safety of ACE inhibitors and felodipine ER and higher than the incidence of adverse events with HCTZ [15]. In our study the interruption due to adverse events in patients treated with losartan was 4.1 % compared with 2.3 % in meta-analysis of controlled clinical trials [19].

## Conclusion

In this double-blind comparison, losartan 50–100 mg once daily exhibited substantial antihypertensive efficacy. It was comparable with metoprolol 50–100 mg twice daily. Both drugs were combined with low-dose HCTZ in patients in whom normal siDBP was not achieved after monotherapy. Both drugs showed similar safety profiles.

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