**Efficacy of losartan and combination of losartan plus hydrochlorothiazide for high blood pressure treatment**

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Hypertension is one of the most common cardiovascular risk factors in adult population. Even values of high normal blood pressure are linked to increased risk of major cardiovascular events and only minority of patients reach the target values with antihypertensive medications prescribed. We wanted to demonstrate the efficacy and safety of treatment with losartan and/or combination of losartan plus hydrochlorothiazide in middle aged population with most frequent cardiovascular risk factors. We conducted a multicenter, prospective, observational, non-randomized study over 10 weeks in patients with essential hypertension whose blood pressure was not adequately controlled despite previously prescribed antihypertensive therapy. Main outcome parameters were systolic and diastolic blood pressure reduction and the rate of normalization of blood pressure at study end, comparing to baseline. 595 patients were included in the study, 313 men and 282 women (1 of the participant’s sex was not determined), with mean age of 63.1 ± 10.0 years. Patients received losartan and/or losartan plus hydrochlorothiazide instead or on top of their previous antihypertensive medications. Average blood pressure was lowered from (158 ± 13)/(95 ± 9) mmHg to (137 ± 10)/(84 ± 8) mmHg and (157 ± 15)/(92 ± 9) mmHg to (136 ± 12)/(82 ± 8) mmHg in non-diabetic and diabetic patients respectively ($P<0.05$). Average blood pressure reduction was 21/11 mmHg for non-diabetic patients while reduction of blood pressure for diabetic patients was 20/11 mmHg. Target blood pressure attainment rates were higher in non-diabetic patients. From our results we may conclude that losartan and/or combination of losartan plus hydrochlorothiazide are effective and potent antihypertensive agents and could be used in high risk non-diabetic and diabetic patient due to its neutral and some beneficial metabolic effects.

**Key words:** Losartan, hydrochlorothiazide, high blood pressure.

**INTRODUCTION**

Arterial hypertension is one of the most common cardiovascular risk factors in adult population [Summary of the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines, 2007; Stergiou et al., 2004; Kearney et al., 2005; Kannel, 1996], especially for myocardial infarction and stroke (Bronner et al., 1995; Kjeldsen et al., 2001). Arterial hypertension leads to left ventricular hypertrophy (LVH) which strongly predicts myocardial infarction, stroke, and cardiovascular death (Koren et al., 2001; Mensah et al., 1993) in the general population (Levy et al., 1990; Bikkina et al., 1994) and patients with coronary artery disease (Ghali et al., 1992). The duration of hypertension and values of blood pressure influence the risk of stroke, heart failure, atherosclerosis and kidney disease (Kannel, 1996). The Framingham Heart Study showed that people with blood pressure (BP) values of 130 to 139/85 to 89 mmHg have more than two times the risk for developing cardiovascular diseases, than patients with BP ≤ 120/80 mmHg (Vasan et al., 2001).
The prevalence of arterial hypertension is immense, especially in Europe. Age- and sex-adjusted prevalence of hypertension was 28% in the North American countries and 44% in the European countries at the 140/90 mmHg threshold (Wolf-Maier et al., 2003). Although hypertensive patients are readily recognized, only minority of them reach blood pressure goals with treatment, especially in Europe. Compliance to pharmacological therapies plays an important role in achieving blood pressure goals in hypertensive patients (Wolf-Maier et al., 2004). Inadequate compliance of some patients may be due to unpleasant side effects of prescribed drugs (Bangalore et al., 2007) or too many different medications prescribed.

The European Guidelines recommend prompt treatment of patients affected by hypertension to reduce cardiovascular risk (Summary of the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines, 2007). Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretics, beta-blockers, calcium channel-blockers, alpha adrenergic blockers and seldom other antihypertensive agents may be used to treat arterial hypertension (Summary of the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines, 2007; Stergiou et al., 2004). When arterial hypertension is diagnosed, the target blood pressure values are rarely achieved by only one antihypertensive medication. Because of that, there are several fixed dose-combinations now available on the market.

Since approval of first ARB – losartan (L) for clinical use, several other ARBs emerged as potent antihypertensive medications (valsartan, candesartan, irbesartan, telmisartan, and olmesartan) (Oparil et al., 2001; Wen-peng et al., 2011). L is an ARB, whose efficacy and potency was clearly established in LIFE study, which showed significant reduction, not only of the blood pressure, but also of the cardiovascular morbidity and mortality comparing to atenolol (Lindholm et al., 2002; Dahlöf et al., 2002). Hydrochlorothiazide (H), a benzothiazide diuretic, inhibits tubular sodium and chloride reabsorption and with that promotes natriuresis. Although its exact mechanism of action is unknown, H has complementary effect to ARB that makes them a good combination as antihypertensive regiments (Kjeldsen et al., 2005; Brunner et al., 1980).

The aim of this study was to demonstrate the efficacy of a prompt pharmacologic treatment with L or combination of losartan plus hydrochlorothiazide (LH) as a mono-therapy or add-on therapy in middle aged population with most frequent cardiovascular risk factors.

**MATERIALS AND METHODS**

In open-label, multicenter, prospective, observational, non-interventional, non-randomized and post-marketing surveillance study, we evaluated effectiveness of treatment with L alone (maximum daily dose of 100 mg) and the fixed combination of LH (maximum daily dose of 100 mg/25 mg) in reaching blood pressure goals. L or LH served either as mono-therapy, exchange for an existing therapy or add on therapy. Study was approved by the Slovenian ethic committee in research and was observational and neither randomized, nor blind. Every patient served as a control to himself. Study had begun in September 2008 and ended in November 2009. The follow up of individual participant in the study was 8 to 12 weeks (median of 10 weeks). All the participants were recruited in Slovenia. 75 physicians (specialists of internal medicine, primary care physicians) recruited up to 10 consecutive patients for the study. Only adult patients (18 years or older) were included after they signed their informed consent about participation in the study. The decision on which of the studied medication was prescribed to an individual patient and the way in which physicians controlled the course of treatment and which concurrent medication they prescribed, was not influenced. All the adverse events were obliged to be reported to the manufacturer, who then forwarded the report in a standardized form to the relevant authorities. Two criteria (inclusion and exclusion criteria) were used in this study. Inclusion criteria entail adult patients who: (1) have known essential hypertension, or (2) are already treated for arterial hypertension comprising (a) arterial blood pressure ≥ 140/90 mmHg, (b) diabetes and arterial blood pressure ≥ 130/80 mmHg, or (c) high or very high risk regarding their risk stratification and arterial blood pressure ≥ 130/80 mmHg; whereas exclusion criteria entail: (1) adequately controlled blood pressure regarding their risk stratification, (2) known side effects on L or LH, or (3) known hypersensitivity to L or LH.

At first visit and inclusion in the study we assessed the risk factors for cardiovascular disease (age, arterial blood pressure, dyslipidemia, body mass index (BMI), waist circumference and smoking) (Table 1). Blood pressure was taken with available monometer with upper-arm cuff in the individual physicians practice after five minutes in a sitting position. The average of three blood pressure measures was accounted, which was always measured on the same individual upper-arm. From blood samples, which were taken at inclusion in the study, values of total cholesterol (CH), low density lipoproteins (LDL), high density lipoproteins (HDL), fasting blood glucose level, glycosylated hemoglobin (HbA1C), serum potassium, serum creatinine were determined. Signs of target organ damage were accounted if they were already stated in the patients chart (their last measurement). At the end of the study arterial blood pressure, BMI and waist circumference were measured and blood was taken to asses metabolic effect of treatment (CH, LDL, HDL, fasting blood glucose, HbA1C, serum potassium and serum creatinine).

We used paired Students t-test to calculate the statistical significance of the differences between all the measured variables between the beginning and the end of the study. All data was expressed as means ± SD. Statistical significance was set at P<0.05. The analysis was performed with the statistical software SPSS 17.0 for Windows.

**RESULTS**

**Baseline characteristics**

The total number of patients included was 595; there were 313 men and 281 women (1 of the participant’s sex was not determined). 15 patients did not finish the study or the protocol was not filled correctly. In total cohort, men were more frequent than women. The mean age of the patient in the study was 63.1 years (±10 years), ranging from 24 to 87 years (Table 1).

Among those who had an echocardiography and Doppler ultrasound of carotid arteries done before the
Table 1. Baseline characteristics. BMI – Body mass index.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>60.9</td>
<td>65.5</td>
</tr>
<tr>
<td>Average BMI (kg/m²)</td>
<td>29.6</td>
<td>29.3</td>
</tr>
<tr>
<td>Average Waist circumference (cm)</td>
<td>101.8</td>
<td>94.3</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>51.9</td>
<td>46.6</td>
</tr>
<tr>
<td>No diabetes (%)</td>
<td>48.1</td>
<td>53.4</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>25.5</td>
<td>24.7</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>67.2</td>
<td>61.8</td>
</tr>
<tr>
<td>Early cardiovascular death in family (%)</td>
<td>36.1</td>
<td>39.9</td>
</tr>
<tr>
<td>Abdominal obesity (%)</td>
<td>57.7</td>
<td>57.5</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>55.8</td>
<td>59.1</td>
</tr>
</tbody>
</table>

Antihypertensive therapy in the study

- Patients were included in the study mostly due to inadequate blood pressure control on their medical treatment or ACEI intolerance. Many different antihypertensives were used: ACEI, ARB, calcium channel blockers, diuretics, beta blockers and alpha blockers (Graph 1). 94.4% of all patients were treated with antihypertensive medications prior to study entry. At the beginning of the study 36.2% had only one antihypertensive agent, 38.7% had two, 16% had three and 2% had 4 antihypertensive agents. The majority of included patients had some co-morbidities and therefore concomitant medications. At inclusion, 66.9% of participants did not have any adverse effects of their treatment before inclusion in the study. The most common co-morbidities were: heart disease (26.8%), peripheral vascular disease (14.3%), cerebrovascular disease (9.9%), renal disease (8.6%) and retinopathy (7.3%) (Table 2). The patients’ compliance to the treatment was not assessed.

Antihypertensive pretreatment and treatment

- Patients were included in the study mostly due to an inadequate blood pressure control on their medical treatment or ACEI intolerance. Many different antihypertensives were used: ACEI, ARB, calcium channel blockers, diuretics, beta blockers and alpha blockers (Graph 1). 94.4% of all patients were treated with antihypertensive medications prior to study entry. At the beginning of the study 36.2% had only one antihypertensive agent, 38.7% had two, 16% had three and 2% had 4 antihypertensive agents. The majority of included patients had some co-morbidities and therefore concomitant medications. At inclusion, 66.9% of participants did not have any adverse effects of their treatment before inclusion in the study. The most common co-morbidities were: heart disease (26.8%), peripheral vascular disease (14.3%), cerebrovascular disease (9.9%), renal disease (8.6%) and retinopathy (7.3%) (Table 2). The patients’ compliance to the treatment was not assessed.
Table 2. Estimated risk for a major cardiovascular event in 10 years at baseline.

<table>
<thead>
<tr>
<th>Estimated risk for major cardiovascular event in 10 years (%)</th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>10.1</td>
<td>13.8</td>
<td>12.4</td>
</tr>
<tr>
<td>15 – 20</td>
<td>27.6</td>
<td>22.9</td>
<td>25.4</td>
</tr>
<tr>
<td>20 – 30</td>
<td>31.7</td>
<td>35.8</td>
<td>33.6</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>30.6</td>
<td>27.6</td>
<td>28.5</td>
</tr>
</tbody>
</table>

![Graph 2. Usage of L or LH in different dosages.](image)

Usage of L or LH regarding their dose before inclusion in the study, changes to antihypertensive therapy at 1st visit and antihypertensive therapy at 2nd visit of all participants in the study. L – losartan, LH – losartan + hydrochlorothiazide;

adverse effect of their antihypertensive treatment was dry cough in 24.4% (if they were treated with ACEI) while all other side effects were present in 8.7%. L was introduced most frequently in 100 mg (47%) and LH in 100/25 mg (31%). At the end of the study the most frequently used doses of L were 100 mg (46%) and LH 100/25 mg (34%) (Graph 2).

**Blood pressure**

Average blood pressure at the beginning of the study of all non-diabetic participants was (158 ± 13)/(95 ± 9) mmHg and (157 ± 15)/(92 ± 9) mmHg for diabetic patients, respectively. At the end of the study, the average blood pressure was (137 ± 10)/(84 ± 8) mmHg for non-diabetic patients and (136 ± 12)/82 ± 8 mmHg for diabetic patients. At the beginning of the study, 51% of non-diabetic patients had systolic blood pressure (SBP) over 160 mmHg and 45% had diastolic blood pressure (DBP) over 100 mmHg. Only 5% of the non-diabetic patients had SBP below 140 mmHg and 6% had DBP below 90 mmHg. At the end of the study 50% of the non-diabetic patients had SBP under 130 mmHg and 58% had DBP below 90 mmHg. At the beginning of the study 44% of diabetic patients had SBP over 160 mmHg and 28% had DBP over 100 mmHg. Only 1% of the diabetic patients had SBP below 130 mmHg and 17% had DBP below 80 mmHg. At the end of the study 21% of diabetic patients had SBP under 130 mmHg and 66% diastolic
blood pressure under 80 mmHg (Graph 3, Graph 4).

**Laboratory values**

Treating non-diabetic patients with L and/or LH on top of or instead of their former therapy made no significant differences on waist circumference, CH, HDL, fasting blood glucose, serum potassium and creatinine ($P > 0.05$). There was a statistical significance in improvement of LDL levels and BMI after treatment with L and/or LH ($P < 0.05$). Average LDL levels were reduced from 3.3 to 3.0 mmol/L, while average BMI levels were reduced from 28.4 to 27.7 kg/m². Treating diabetic patients with L and/or LH on top of or instead of their former therapy made no significant differences on BMI, waist circumference, HDL, HbA1c, serum potassium and creatinine levels ($P > 0.05$). There was a statistical significance in improvement in CH, LDL and fasting blood glucose levels after treatment with L and/or LH ($P < 0.05$). Average CH levels were reduced from 5.8 to 5.3 mmol/L, average LDL levels were reduced from 3.5 to 3.0 mmol/L and average fasting blood glucose levels were reduced from 7.1 to 6.4 mmol/L.

**Physician’s perspective on efficacy of L and LH**

Two main reasons for a change in antihypertensive therapy at the beginning of the study where dry cough and inadequately controlled blood pressure. 85% of the physicians were satisfied with L and/or LH treatment at the end of the study, because blood pressure goals were reached. 15% of the physicians were unsatisfied because of different causes, the most frequent of them were the inadequately controlled arterial blood pressure (7%) and other causes – not specified (8%).

**DISCUSSION**

This study examined the antihypertensive efficacy of 10 week treatment with L and/or LH as mono therapy or as add on antihypertensive therapy in middle aged population with most frequent cardiovascular risk factors. Since hypertension is a multi-factorial disease, combining therapies with different mechanisms of action, can additively reduce blood pressure. The benefit of adding L to H may be explained by the fact that diuretics decrease the intravascular volume activating renin-angiotensin-aldosteron system resulting in a diminished antihypertensive response, on which L works and blocks it. Regarding that L in combination with H has additional BP lowering effects compared to the mono therapy (Kjeldse et al., 2005; Brunner et al., 1980). The endpoint study available, serving as the basis of approval of the high-dose L or LH combination, was the randomized
controlled Losartan Intervention For Endpoint reduction in hypertension (LIFE) study (Lindholm et al., 2002; Dahlöf et al., 2002).

With the exception of two German (Bönner et al., 2009; Förster et al., 2007), one Spanish (Coca et al., 2002) and one Japanese (Saruta et al., 2007) study, to our knowledge, there are no current data on the efficacy and safety of the unselected “every-day” care patients in primary care settings. However, high-dose of L and LH is less documented than lower doses of L and LH.

Efficacy

The results of the study showed that the treatment with L or LH in middle aged population with most frequent cardiovascular risk factors is very effective, which was also shown before (Kjeldse et al., 2005; Brunner et al., 1980). The average reduction of blood pressure for non-diabetic patients was 21/11 mmHg and 20/11 mmHg for diabetic patients, respectively. The mean reduction of SBP and DBP was comparable to other studies already done. Fixed-dose combination improves medication compliance for 24 to 26% (Bangalore et al., 2007). These data are in agreement with the well known tolerability of other ARB´s including losartan as mono-therapy or combination therapy.

Target level achievement

It is well known that arterial hypertension is readily recognized in European countries, but blood pressure goals are reached only in minority patients treated (Wolf-Maier et al., 2003; Wolf-Maier et al., 2004). It seems that the same is true for Slovenia. Regarding that majority of the patients included in the study were already known and treated for arterial hypertension (only 5% of patients included in the study did not have prior antihypertensive therapy), SBP goals (SBP below 140 mmHg) at inclusion in the study were achieved in only 5% and DBP goals (DBP under 90 mmHg) in only 18% of non-diabetic patients (Graph 3). Of those who have, besides hypertension also diabetes, only 1% had SBP and only 17% had DBP within the target limits at inclusion (arterial blood pressure below 130/80 mmHg) (Graph 3, Graph 4). Even though that L and LH substantially lowered blood pressure during the study, SBP goals were reached in 50%, while DBP goals were reached in 69% of those who had hypertension without diabetes. In patients that had high blood pressure and diabetes, DBP goals were reached more easily than SBP goals with L or/and LH treatment. Only 21% of patients that had arterial hypertension and diabetes reached SBP goals and 66% reached DBP goals. The reason for that may be in greater arterial wall stiffness in patients with arterial hypertension and diabetes.

Effects of treatment with L and/or LH on other measured parameters

There were no important changes in serum potassium, creatinine and HDL levels in non-diabetic and diabetic patients (P>0.05). Waist circumference in all the included
patients was also not significantly changed (P>0.05), while BMI (the reduction was rather small) was significantly lower at the end of the study in non-diabetic patients (P<0.05). It is interesting that fasting serum glucose level was not a subject of significant change during the day, especially in diabetic patients, while HbA1c represents serum glycemic control on a longer term. HbA1c at the end of the study was not significantly changed in diabetic patients (P>0.05), so we may conclude that L and LH are not affecting the metabolism of glucose even though our study showed an improvement in the serum glucose after treatment with L and/or LH in diabetic patients. We also found an improvement in serum LDL levels in all the patients at study end (P<0.05), which is not in concordance with studies done before (Moen et al., 2005). It is interesting that our study showed an improvement in total serum cholesterol in diabetic patients (P<0.05), while there were no improvement in non-diabetic patients. Although the reduction of total serum cholesterol in diabetic patients and reduction of LDL levels in all included patients reached the level of significance, they were rather small. Other potentially beneficial effects of L and LH were not assessed in this study. However, in studies conducted before it was shown, that L has a capacity to reduce microalbuminuria, because of blocking the renin-angiotensin-aldosteron system largely independent of its pressure lowering effect, which makes this agent particularly suitable for patients with renal disease (Brenner et al., 2001).

Methodological considerations

When interpreting the present study, certain methodological aspects have to be taken into account. Selection bias is to be expected despite physicians being requested to include eligible patients consecutively. The trial was not controlled, so the placebo effect cannot be accounted for. Long term influence of the treatment on mortality, target organs ischemia and heart failure could not be analyzed from our data because the duration of the study was only 12 weeks at most. Laboratory data was measured only twice and only approximately 10 apart. Some of the laboratory values were measured only once, so they could not be compared to their previous value and had to be excluded. We also did not monitor a 24h antihypertensive profile, so we cannot say anything about sustainment of antihypertensive effect of L and LH during the day.

Conclusions

From our results we may conclude that losartan and/or combination of losartan plus hydrochlorothiazide are effective, potent antihypertensive agents and could be used in high risk non-diabetic and diabetic patients due to its neutral and some beneficial metabolic effects.

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