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Full Length Research Paper

Safety and efficiency of valsartan and combination of valsartan plus hydrochlorothiazide for high blood pressure

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The essential hypertension is one of the most common cardiovascular risk factors in adult population. The duration of hypertension influences the risk of stroke, heart failure, atherosclerosis, and kidney disease. Diuretics, beta blockers, calcium-antagonists, ACE-inhibitors, and sartans may be used to treat arterial hypertension. In this study, the efficacy and safety of a prompt pharmacologic treatment with valsartan (VAL) or combination of valsartan plus hydrochlorothiazide (VAL/HYCT) in middle aged population was demonstrate with the most frequent cardiovascular risk factors. The results of the 4 months study period showed that treatment with VAL or VAL/HYCT in middle aged 1059 patients significantly reduce the systolic and diastolic blood pressure. Average systolic and diastolic blood pressure were lowered from 161.2 (±16.5) and 92.9 (±9.5) mmHg to 136.1 (±12.5) and 81.6 (±7.8) mmHg, respectively. Side effects were observed only in few patients: elevated serum creatinine (4.6%), elevation of HbA1c (1%) and serum potassium values (0.3%). It may be concluded that VAL or VAL/HYCT is safe and very effective potent antihypertensive drug.

Key words: Valsartan, hydrochlorothiazide, high blood pressure.

INTRODUCTION

Hypertension is defined as a systolic blood pressure (SBP) of > 140 mmHg and/or diastolic blood pressure (DBP) of > 90 mmHg. It is one of the most common cardiovascular risk factors in adult population (Kearney et al., 2005; Ong et al., 2007; Fields et al., 2004). The most common is essential hypertension with no known cause. Secondary hypertension is usually due to a renal disorder. Often, no symptoms develop unless hypertension is severe or long-standing. The duration of hypertension and values of blood pressure influence the risk of stroke, heart failure, atherosclerosis and kidney disease (Kannel, 1996; Vasan et al., 2001; Lindeman et al., 1984; Wollom and Gifford, 1976). The Framingham Heart Study showed that people with blood pressure (BP) value of 130 to 139/85 to 89 mmHg have more than two times more risk for cardiovascular diseases as patients with BP≤ 120/80 mmHg.

In the United States (US), about 65 million people have hypertension, 59% are being treated, and only 34% have adequately controlled BP (Kearney et al., 2005). Lack of diagnosis, inadequate treatment and poor compliance to pharmacologic therapies are the main reasons for poor control of BP. Inadequate compliance of some patients may be due to unpleasant side effects of prescribed drugs (Bangalore et al., 2007; Beto and Bansal 1992).

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 for the Management of

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Arterial Hypertension, 2007; Bonny et al., 2008). Diuretics, beta blockers, calcium-antagonists, angiotensin-converting enzyme inhibitors (ACEI), and sartans may be used to treat arterial hypertension (Kearney et al., 2005; Plum et al., 1998; Cutler et al., 1989).

The aim of this study was to demonstrate the efficacy and safety of a prompt pharmacologic treatment with valsartan (VAL) or combination valsartan plus hydrochlorothiazide (VAL/HYCT) in middle aged population with most frequent cardiovascular risk factors.

MATERIALS AND METHODS

In open-label, multicenter, prospective, observational, non-interventional and post-marketing surveillance study, we evaluated safety and effectiveness of the treatment with valsartan 320 mg alone and the fixed combination of valsartan and hydrochlorothiazide 320 mg/12.5 mg or 320 mg/25 mg in reaching blood pressure goals. Duration of treatment in the study was 4 months. Paired Students t-test was used to calculate the statistical significance of the differences between the systolic and diastolic blood pressure at the end of the study and the systolic and diastolic blood pressure at the beginning of the experiment between patients that were treated with VAL alone or/and with VAL/HYCT. All data was expressed as means±standard deviation (SD). Statistical significance was set at $P<0.05$.220 doctors recruited up to 5 patients for the study. The total number of patients analyzed was 1059; they were 527 men and 530 women. The mean age of the patients in the study was 63.5 years (SD=11 years), ranging from 28 to 94.

Besides high blood pressure (92%), the most frequent cardiovascular risk factors were dyslipidemia (62%), diabetes mellitus (34%), obesity (40%), and smoking (20%). The number of existing risk factors per patient is given in Figure 1. Almost 60% of the patients have more than 4 (4/9) risk factors for atherosclerosis.

For the patients in primary prevention (73%), total absolute risk for development of coronary disease in the next years was more than 20%. In the group of patients for secondary prevention (27%), coronary artery disease, periferial artery disease or cerebrovascular disease were found in 57, 16 and 24%, respectively. The patients were included in the study mostly due to ACEI intolerance or inadequate blood pressure control on their medical treatment. Many different antihypertensive combinations were used. Most frequently ACEI, angiotensin receptor II blockers (ARB), calcium channel blockers, diuretics and beta blockers were used. 17.8% patients were treated with ACEI as mono-therapy. Most of the patients have some co-morbidity and therefore concomitant medications, most frequently, aspirin and statins were administrated. There were some changes of medical treatment in patients at inclusion to the study. VAL/HYCT was introduced most frequently in 160/12.5 mg (40%) and VAL 320 mg (30%) doses. After the final treatment the most frequent used doses of VAL/HYCT were 160/12.5 mg (24.7%) and 320/12.5 mg (34.5%). The changing of the dose is presented in Figure 2.Patients' compliance to the treatment with VAL/HYCT was good, more than 93% of the patients take tablets nearly always (>90%). The patients' compliance with the treatment is presented in Figure 3.

RESULTS

There were statistical significant difference between the systolic and diastolic blood pressure at the end of the study and the systolic and diastolic blood pressure at the beginning of the experiment between patients that were treated with VAL alone or/and with VAL/HYCT.

Average systolic blood pressure at the beginning of the study was 161.2 (±16.5) mmHg and at the end of the study was 136.1 (±12.5) mmHg ($P<0.05$), average diastolic blood pressure was 92.9 (±9.5) mmHg and at the end of DBP was 81.6 (±7.8) mmHg ($P<0.05$).

These patients (65%) had SBP over 160 mmHg or DBP over 100 mmHg. Only 3.5% of the patients had BP below 140/90 mmHg. At the end of the study, only 5% of the patients have SBP over 160 mmHg or DBP over 100 mmHg. 27% of the patients have BP below 120/80 mmHg and additional 35% below 140/90 mmHg. The comparison of the blood pressure distribution between the first and the last visit is as shown in Figure 4.

The most frequent non-serious adverse event reported was elevated serum creatinine (4.6%), elevation of HbA1c (1%) and serum potassium values (0.3%). All together non-serious adverse effects were reported in 79 cases (7.5%[).

DISCUSSION

The results of this study showed that treatment with VAL or VAL/HYCT in middle aged population with most frequent cardiovascular risk factors is safe, very effective and with good compliance (Bangalore et al., 2007; Ruvolo et al., 2010; Mallion et al., 2003; Pool et al., 2007; Wagstaff, 2006). There were no important changes in HbA1c, serum creatinine and serum potassium values. Side effects were observed only in 7.5% patients. The reduction of SBP and DBP was excellent. The average reduction of SBP was 25 mmHg and DBP was 11 mmHg.

Hypertension is a multifactor disease. Combining therapies with different mechanisms of action can additively reduce BP (Schmidt et al., 2001). VAL blocks the activation of angiotensin II receptors. This causes vasodilatation, reduces secretion of vasopressin, secretion and production of aldosterone, what reduces blood pressure. VAL and HYCT in combination has additional BP lowering effects as compared to the monotherapy (Pool et al., 2007; Ruvolo et al., 2010; Mallion et al., 2003; Weir et al., 2007). The benefit of adding HYCT to VAL may be explained by the fact, that diuretics decrease intravascular volume and activate renin-angiotensin-aldosterone system resulting in a diminished antihypertensive response.

Fixed-dose combination of VAL/HYCT was used due to low side effects; the treatment compliance was good in more than 92% of the patients. Fixed-dose combination improves medication compliance for 24 to 26% (Bangalore et al., 2007).

It may be concluded that VAL or VAL/HYCT is a potent antihypertensive medication. It is indicated both in non diabetic and diabetic patient due to its potency and

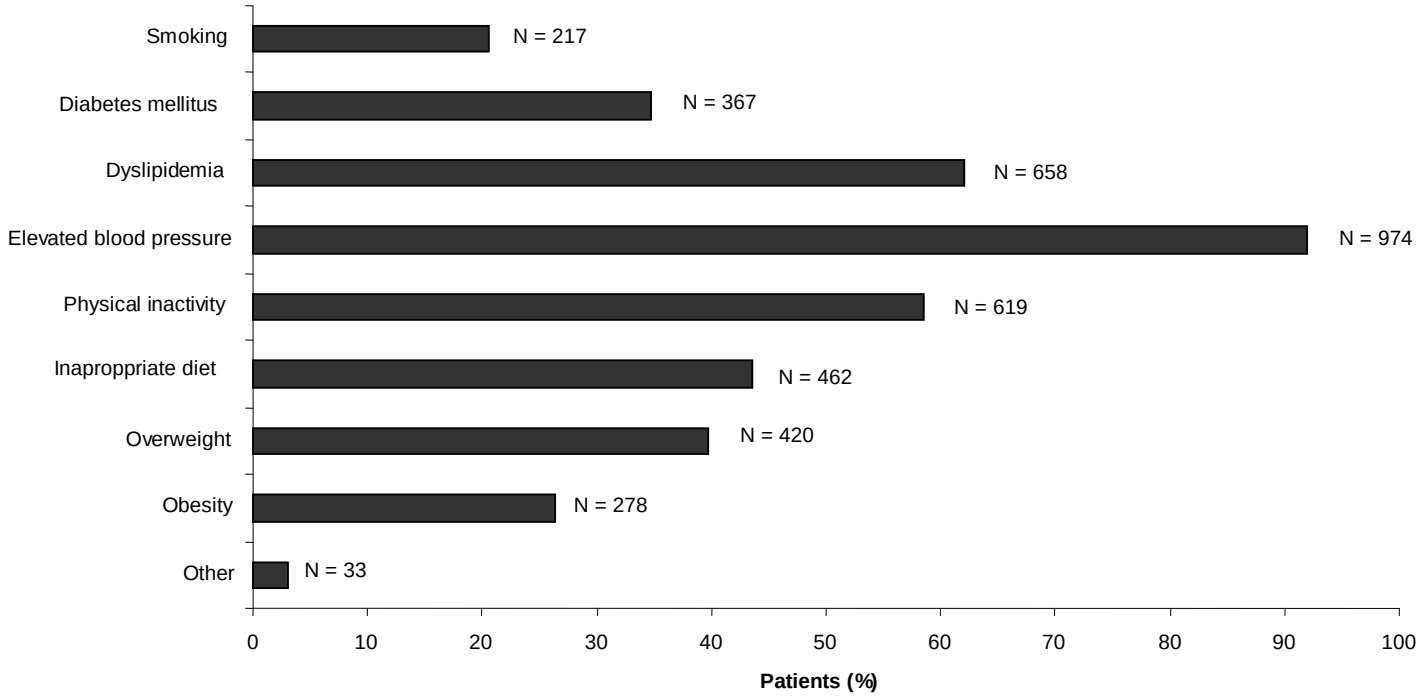

Figure 1. Existing risk factors.

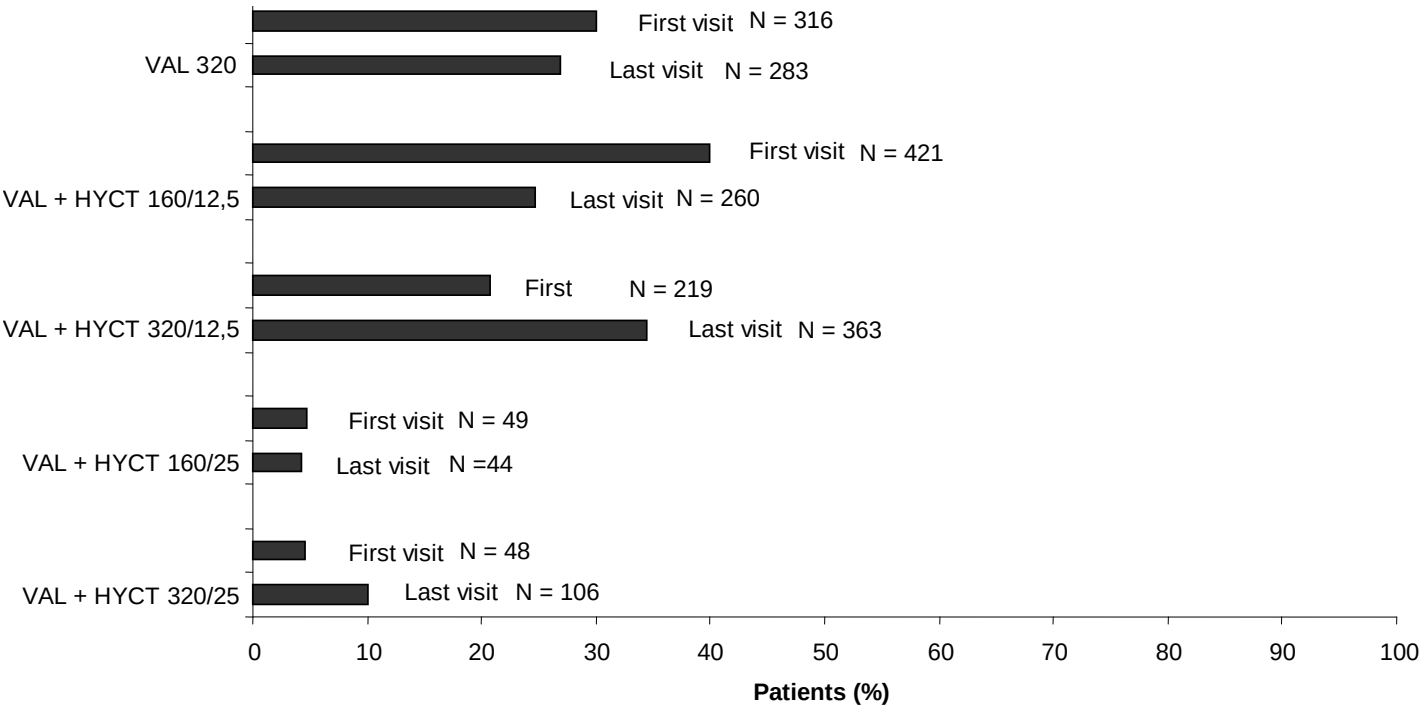

Figure 2. VAL/VAL+HYCT dose changing.

metabolic neutral action. Long term influence of the treatment on mortality, target organs ischemia, heart failure and 24 h antihypertensive profile could not be analyzed from our data because the duration of the study

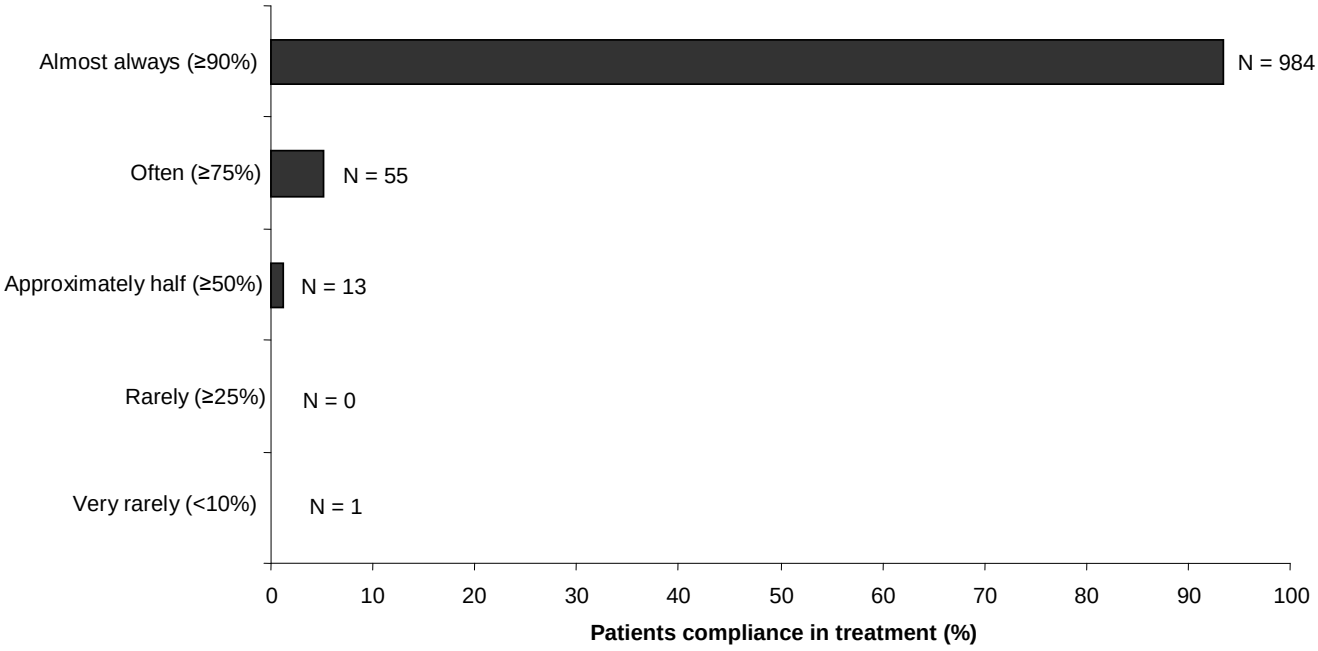

Figure 3. Patient compliance with treatment.

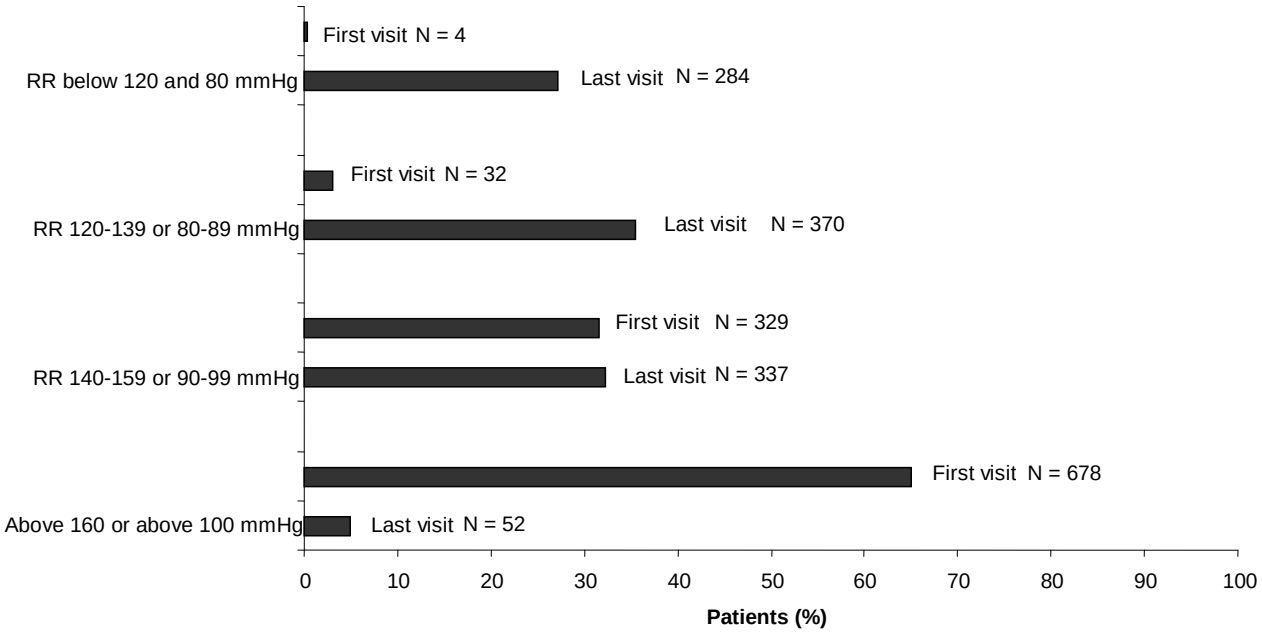

Figure 4. Comparison of blood pressure values.

was only four months.

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