Hypertension and valsartan

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Abstract

Hypertension, which is pointed to be the most frequent cause of death in the World and in Turkey and defined by the World Health Organization as global health crisis and the prominent risk factor for cardiovascular diseases, is a problem threatening public health. Renin-angiotensin system (RAS) plays an important role in pathophysiology and in turn treatment of the disease. The drugs suppressing RAS are recommended both for monotherapy and combinations. Together with the blood pressure lowering effects and positive contributions of this group of drugs to the cardiovascular and renal process have been proved by clinical studies. In this review, the recent developments about the hypertension treatment were summarized and the place of valsartan molecule, being an angiotensin receptor blocker in hypertension treatment, was examined in the light of the studies in which the effectiveness, tolerability and safety of valsartan were evaluated. *(Anadolu Kardiyol Derg 2014; 14(Suppl 2): S20-S4)*
Key words: hypertension, angiotensin receptor blockers, valsartan

The World Health Organization classifies hypertension as "a silent killer" and "a global public health crisis" in the global brief on hypertension, published on the occasion of World Health Day 2013. Hypertension is a crucial risk factor for cardiovascular diseases, which is the most frequent cause of death in Turkey and in the world, and is a major threat to public health (1, 2).

Hypertension is considered to be both a significant risk factor for the development and onset of cardiovascular disease. The World Health Organization reported that 56 million people died in 2008, of whom 36 million died due to non-communicable diseases (cardiovascular diseases, cancer, respiratory diseases, and diabetes); cardiovascular diseases account for 17.3 million of these deaths. Of these cardiovascular deaths, 7.3 million were due to coronary heart diseases and 6.1 million were due to stroke. Hypertension was responsible for 45% of deaths due to coronary heart diseases and for 51% of deaths due to stroke. Mortality due to hypertension was reported as 9.4 million annually. Moreover, hypertension was the leading risk factor for death, followed by tobacco use and diabetes mellitus (3).

Despite the fact that hypertension is a reversible risk factor and is treatable, target blood pressure cannot be achieved in more than half of patients. Data from Turkey and all over the world show that the hypertensive population continues to increase due to the growing aging population and negative effects of technological development. Social conditions that are undesirable but almost impossible to control, such as an aging population, globalization of unhealthy lifestyles, rapid and unplanned urbanization, educational level, and unbalanced income distribution, predispose many to hypertension. Malnutrition (diets with high salt and/or fat content, inadequate consumption of vegetables and fruits), tobacco use, alcohol abuse, insufficient physical activity, stress, metabolic risk factors, obesity, diabetes, and high lipid levels are defined as behavioral risk factors for the development of hypertension (1, 3).

While the reported number of hypertensive individuals was 972 million in 2000 worldwide, this number is expected to be 1.56 billion by a 60% increase in 2025. On the other hand, improvements in diagnosis and follow-up, the presence of numerous options for antihypertensive medication, and an increased awareness and patient participation in treatment in this age of rapid communication are promising developments in the management of hypertension (4).

Patient incompliance, which can be encountered during treatment of all chronic diseases, decreases treatment success dramatically. All factors affecting the continuation of lifelong treatment should be evaluated carefully. Patient-doctor communication, informing patient, and active patient participation in treatment are critical factors influencing treatment success. During drug selection, efficacy along with tolerability and patient compliance should be considered.

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Hypertension is classified as primary (essential) (90%-95%) and secondary (5%-10%) hypertension. The goal of treatment does not differ in either condition; the aim is to control blood pressure. In endocrine- or renal disease-associated hypertension, antihypertensive treatment may be required. High blood pressure that is not associated with a specific disease is called primary (essential) hypertension and is defined as hypertension of unknown origin. The term "unknown origin" can negatively affect patient compliance to treatment. The cause of essential hypertension, including causal mechanisms, is unknown. Genetic factors, increased cardiac output, peripheral resistance, sympathetic system and RAS system activation, endothelial damage, vasoactive substances, insulin resistance, and low birth weight lead to the development of hypertension (5).

Holistic health management is needed for hypertension because of its complex pathophysiology, being a disease that affects all systems, and the presence of many diseases accompanied by or associated with hypertension. Concurrent diseases, conditions, and risks should be considered while planning pharmacological treatment together with lifestyle changes. The main goal of the treatment targeting blood pressure control is to prevent short- and long-term cardiovascular, cerebral, and renal complications. Clinical trials have demonstrated that, in addition to blood pressure, effects related to heart, brain, and kidney protection are decisive in treatment.

Current guidelines on hypertension treatment recommend lifestyle changes as first-line management before and during pharmacological treatment. Lifestyle changes include salt restriction, weight control, exercise, restricted alcohol use, and smoking cessation. It is recommended that pharmacological treatment should be planned together with lifestyle changes and that if blood pressure is not controlled within 1 month, the treatment strategy should be changed (6, 9). Clinical studies revealed that antihypertensive treatment decreases stroke by 35%-40%, myocardial infarction by 20%-25%, and heart failure by over 50%. Compared to other interventions, hypertension treatment is an option with a higher cost-benefit ratio (10, 11).

Hypertension and renin-angiotensin system (RAS) blockade

The joint guideline by the European Society of Hypertension and the European Society of Cardiology (the 2013 guideline on arterial hypertension) recommends five main drug groups [(diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs)] equally in monotherapy together with lifestyle changes, unless any compelling indication. ACEIs and ARBs, which provide RAS blockade, are the medications preferred in the majority of specific conditions, such as left ventricular hypertrophy, asymptomatic atherosclerosis, microalbuminuria, renal dysfunction, previous stroke, myocardial infarction, heart failure, atrial fibrillation, end-stage kidney disease, proteinuria, peripheral arterial disease, metabolic syndrome, and diabetes. Initiation of treatment with a combination of two drugs is recommended when a decrease of more than 20 mm Hg in blood pressure is required or in patients with high or very high cardiovascular risk. The preferred dual combinations comprise of RAS blockers with diuretics or RAS blockers with calcium channel blockers. If triple combination therapy is required, a combination of these drugs (RAS blocker, calcium channel blocker, and diuretic) is recommended. The option for a fixed combination in a single tablet has been reiterated in the recent guideline as it decreases the number of drugs and increases patient compliance (5).

The general approach of guidelines on drug and combination selection is similar. The NICE guideline recommends a RAS blocker for monotherapy in patients below 55 years old (ACEIs or ARBs), a calcium channel blocker in patients over 55 years old, a combination of one drug from each of these two groups for a dual combination, and addition of a diuretic as the third drug for a triple combination. In all guidelines, it is agreed that treatment should be initiated with a RAS blocker for hypertension with concurrent chronic kidney disease or diabetes and that if combination therapy is planned, one of the drugs should also be selected from this group. In order to reach target values, two or more drugs are generally needed in two of three patients (6-9).

The effects of RAS blockade on hypertension treatment and on the risk reduction for cardiovascular events have been proven in large clinical trials. The Heart Outcomes Prevention Evaluation (HOPE) (12) study was an important milestone in this issue, followed by studies including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (13), the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) (14), the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) (15), and the ONTARGET (16).

The LIFE study highlighted the importance of ARBs. The superiority of losartan over atenolol, which is commonly used in hypertension treatment, raised doubts on conventional treatment. The VALUE study (15), which compared valsartan with amlodipine, which is accepted as a modern antihypertensive, achieved a significant breakthrough in ARBs.

Activation of angiotensin II, which plays a major role in the pathophysiology of hypertension and cardiovascular disease, is inhibited by RAS blockade; ACEIs and ARBs are involved in this blockade at different points. ACE is involved at the level of conversion of angiotensin I to angiotensin II in the cascade beginning with the conversion of inactive angiotensinogen secreted by the liver to angiotensin I by renin enzyme secreted by the kidney. ACEI inhibits the cascade at this point and the cycle is completed before the formation of angiotensin II. On the other hand, ARBs are activated after the generation of angiotensin II in the cascade. The undesirable effects of angiotensin II occur when it binds to type 1 angiotensin (AT1) receptors. When this receptor is blocked by ARBs, the effects of angiotensin II also disappear. In the 1990s, RAS blockade with ARBs became clearer. Blockade of the receptor provides additional benefits to the treatment. Since the effect of ACE is sustained, the degradation of bradykinin is not inhibited. This is reflected as better tolerabi-

lity in the clinical setting. Coughing caused by ACEIs is not observed because ACE is preserved and the risk of angioneurotic edema, which may be seen rarely and result in fatal outcomes, decreases significantly. Angioneurotic edema is one of the contraindications of ACEIs. There are also receptors apart from AT1 to which angiotensin II can bind. Positive effects are obtained, especially with binding of angiotensin II to the AT2 receptor. Moreover, the conversion of angiotensin II to angiotensin (1-7) [Ang (1-7)], an endogenous regulatory peptide, by ACE2 enzyme has cardiovascular importance. Ang (1-7) has a role in the control of cardiovascular functions and blood pressure through its effects on vasodilatation, natriuresis, diuresis, baroreceptor control, inhibition of angiogenesis, and cell growth (17-20).

All guidelines agree that there is no difference between ACEIs and ARBs in hypertension treatment, although they have different pharmacological characteristics and are activated at different stages of RAS. In order to prevent some questions on ARBs raised by recently published meta-analyses, the 2013 European guideline particularly emphasized this issue. Furthermore, in this guideline, the absence of a difference between the two RAS blockers was emphasized by referring to the ONTARGET (16) study, in which ACEI and ARB were compared.

Nowadays, one of the most important selection criteria for antihypertensive treatment is the benefit-cost ratio. Since tolerability and patient compliance influence the continuation of treatment, they affect pharmacoeconomic outcomes particularly in the treatment of chronic diseases. Good patient compliance increases the rate of blood pressure control and decreases cardiovascular complications and treatment costs (21, 23). ARBs are the drug group providing the highest rate of continuity in hypertension treatment (24).

Although the structural and chemical characteristics of ARBs lead to some differences in their pharmacokinetics, such as half-life, receptor affinity, lipophilicity, and bioavailability, no result raised by these differences has been reflected clinically (25). Despite this, during selection of an ARB, it is advantageous to consider clinical experience and large studies conducted on their effects.

Hypertension and valsartan

Valsartan, which is one of the first members of the ARB group, has been used since 1996 in Europe, since 1997 in the United States of America, and since 1998 in Turkey. It can be combined with hydrochlorothiazide (HCTZ), amlodipine, and aliskiren. The efficacy and reliability of valsartan in hypertension, post-myocardial infarction, and heart failure have been revealed by large clinical trials (15, 26, 27).

Monotherapy

Nixon et al. (28) conducted a meta-analysis that compared valsartan to other ARBs and evaluated the data of 13,110 patients obtained from 31 randomized clinical trials, 12 of which were on valsartan. In that particular study, the effects of valsartan and all other ARBs increased depending on the dose. When the dose of valsartan was increased from 80 mg to 160 mg, the reduction in the mean systolic blood pressure (SBP) increased from 11.52 mm Hg (95% CI: -14.39, -8.70) to 15.32 mm Hg (95% CI: -17.09, -13.63) and when the dose was increased to 320 mg, the reduction in the mean SBP increased to 15.85 mmHg (95% CI: -17.60, -14.12). Reduction in diastolic blood pressure (DBP) was measured as -8.71 mm Hg (95% CI: -9.94, -7.50), 11.33 mm Hg (95% CI: -12.15, -10.52), and 11.97 mm Hg (95% CI: -12.81, -11.16) for the valsartan doses of 80 mg, 160 mg, and 320 mg, respectively. More reductions in SBP and DBP were obtained with 160 mg valsartan than with 150 mg irbesartan. On the other hand, when compared to 16 mg candesartan, more reductions were observed only in DBP with 160 mg valsartan. As a result, it was reported that the antihypertensive effects of 160 mg and 320 mg valsartan were higher than that of 100 mg losartan but similar to other ARBs.

Combination therapy

The efficacy and safety of the combination of valsartan with HCTZ or amlodipine have been demonstrated in various studies (29-37). In addition to achieving a greater antihypertensive effect in combination therapy than in monotherapy, a better side effect profile is also obtained. In the valsartan-diuretic combination, HCTZ-induced hypokalemia is reduced. On the other hand, in the valsartan-calcium channel blocker combination, peripheral edema associated with amlodipine is decreased (29, 30).

Weir et al. (38) analyzed the data of 4,278 patients, who were from nine randomized, double blind, and placebo-controlled clinical trials and evaluated valsartan (at the doses of 80 mg, 160 mg, and 320 mg) and valsartan/HCTZ combinations (at the doses of 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg). At the end of 8 weeks, target blood pressures were achieved by 80 mg valsartan in 32% of the patients, by 160 mg valsartan in 48.4% of the patients, by 320 mg valsartan in 54.2% of the patients, by 160 mg valsartan/HCTZ in 74.6% of the patients, and by 320 mg valsartan/HCTZ in 84.8% of the patients. Moreover, combination of 320 mg valsartan with HCTZ (12.5 mg or 25 mg) resulted in blood pressure control in 75.8% of the stage 1 patients and in 94% of the stage 2 patients.

In hypertension treatment, triple combinations provide higher blood pressure reductions than dual combinations and their side effect profiles are similar (39). Calhoun et al. (40) evaluated the efficacy and safety of the triple combination of amlodipine/valsartan/HCTZ (Aml/Val/HCTZ) for moderate or severe hypertension. Their study also included comparisons of dual combinations of valsartan and an amlodipine/HCTZ combination. The study was single-blinded with a placebo run-in period and had subsequent double-blind treatment periods of 8 weeks. The patients were randomized into the groups of Aml/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, or Aml/HCTZ 10/25 mg, provided that the doses were given once a day. Totally 2,271 patients were randomized; however, only 2,060

patients completed the study. The number of patients for whom blood pressure control was achieved was significantly higher with triple combination than with dual combinations. The rates of blood pressure control were found to be significantly higher with triple combination (85.1%) than with dual combinations of Aml/HCTZ (64.1%), Val/HCTZ (69.6%), or Aml/Val (72.4%) (p<0.0001) (40). In a patient subset of the above-mentioned study, Lacourciere et al. (41) evaluated the ambulatory blood pressures and determined a 24-hour efficacy for all combinations. There are also other studies showing the efficacy and safety of the valsartan-amlodipine combination in different populations (29-32, 34, 36). Among the studies conducted in Turkey and included the real-life data, which evaluated the efficacy and safety of the valsartan-amlodipine single-tablet combination in hypertensive patients, the first one was the PEAK study (Efficacy and safety of the valsartan-amlodipine single-pill combination in hypertensive patients) (42). The PEAK study compared combinations of 160 mg valsartan with 5 mg and with 10 mg amlodipine in 1,184 patients. In the second study, called the PEAK LOW (Efficacy and safety of valsartan/amlodipine single-pill combination in patients with essential hypertension) (43), only the combination of 160 mg valsartan with 5 mg amlodipine was evaluated in 381 patients.

The PEAK study was performed in 166 research centers and the patients were followed for 24 weeks. Hypertensive patients aged >18 years who were already being treated with combinations of valsartan/amlodipine (160 mg/5 mg or 160 mg/10 mg) were included. The measurements were performed in the office in accordance with the guidelines. The higher of the two measurements was recorded. Of the patients, 46% used 5 mg/160 mg of amlodipine/valsartan and 54% used 10 mg/160 mg of amlodipine/valsartan; 662 (56%) patients completed the study. The majority of patients who did not complete the study were those who did not come in for control examinations (416 patients, 35.1%). The mean baseline blood pressures was164.2±0.9 mm Hg /95.8±0.6 mm Hg. Compared to baseline values, the combination therapy significantly decreased SBP by 29.6±0.9 mm Hg and DBP by 14.7±0.6 mm Hg (p<0.001 for both). During the study, 174 adverse events were reported in 150 (12.7%) patients, of which 96.9% were defined as non-serious adverse events. The most common adverse event was edema. The incidence of new-onset edema was 6.7% when all patients receiving 5 mg /160 mg or 10 mg /160 mg of amlodipine/valsartan were evaluated. The blood pressure control rate was 86.9% (p<0.001).

In the PEAK LOW study, the patients using 5 mg/160 mg of amlodipine/valsartan were followed in 30 research centers for 12 weeks. It was observed that SBP decreased from 162.6±16.6 mm Hg to 131.6±11.5 mm Hg and DBP decreased from 94.0±13.2 mm Hg to 79.7±7.6 mm Hg. At the end of the study, the blood pressure control rate was 82.0% and the response rate was 92.6%. Of the patients, 327 completed the study. Totally, 12 adverse events were observed in 12 (3.2%) patients. The most common adverse event was edema (1.3%) and there was no severe adverse event. Patient compliance was found to be about 99%, the blood pressure control rate was 82.0%, and the response rate was 92.6% (43).

The aim of hypertension treatment is to reduce the risk of cardiovascular, cerebrovascular, and renal complications by blood pressure control. Patient compliance and continuity of treatment, which we encounter in all chronic diseases, affect the results. Valsartan and its combinations are beneficial treatment options, based on data of large clinical trials and clinical experience.

Conflict of Interest: Prof. Yağız Üresin is a member of Novartis' Advisory Board and Dr. Pınar Kızılırmak is a Novartis employee.

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