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Hypertension therapy and cardiovascular protection. Effects of angiotensin II receptor block with Valsartan

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Abstract. – *Objectives:* **Arterial hypertension and its pharmacological control are discussed in view of the high cardiovascular risk due to lack of target blood pressure achievement. It is, therefore, underlined the need for a highly effective therapy, able to provide protection from organ damage through a marked antihypertensive activity. In addition to this basic property, also compliance of the patient to therapy is needed, in order to avoid that the effects of therapeutic measures should result fruitless.**

Discussion and Conclusions: **An answer to this problem appears now offered by a recent class of antihypertensive agents, the angiotensin II receptor blockers (ARBs). Among them valsartan has been described, providing an overview of methodologically adequate clinical studies, evaluating the efficacy, even at long-term, and safety. Valsartan has been compared with other antihypertensive agents of proven efficacy, mainly amlodipine, showing a better clinical profile. A wide room was finally left to the problem of adherence to therapy, whose lack is associated very frequently with marked increases in cardiovascular risk, due to absent or insufficient blood pressure control. This implies significant increases of health costs, as documented in numerous Countries, mainly following the higher need for hospitalization. On the other hand, it is also well documented the pharmacoeconomic benefit associated to ARBs use, particularly with valsartan.**

Key Words:

Hypertension, Cardiovascular diseases, Renin Angiotensin System, ACE Inhibitors, Angiotensin Receptor Blockade, Valsartan.

Introduction

It is widely recognized that cardiovascular diseases are the leading cause of death worldwide[1-3]. Their incidence is expected to continue to increase with the increasing mean age of population and according to a better life expectancy[1,2]. Arterial hypertension represents the main cause of cardiovascular disorders, such as myocardial infarction, ischemic stroke, heart failure, renal insufficiency, and other clinical events[1,2]. Therefore, an effective antihypertensive pharmacotherapy is clearly needed, in addition to proper lifestyle changes, in order to provide not only symptomatic relief but also (and particularly) a global cardiovascular protection[1].

Among the different causes of cardiovascular diseases, hypertension is one of the most preventable factors: in fact an effective antihypertensive drug therapy has been shown to reduce the risk of stroke by 34% and the risk of heart failure by 21% in randomized controlled clinical trials[4-7]. Greater arterial blood pressure reductions result in improved clinical outcomes[8].

The cautious therapeutic approach, planning to start antihypertensive treatment at low dose and titrating afterwards the optimal dose ("start low, go slow"), cannot be further recommended, at least in high-risk patients.

Randomized controlled clinical trials showed that: (1) the time to start an effective antihypertensive therapy may significantly influence cardiovascular outcomes; (2) to obtain optimal results in cardiovascular protection, aggressive antihypertensive therapies are needed, able to attain very tight blood pressure targets[8].

According to the guidelines of JNC 7 (Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure)[9,10], in patients requiring blood pressure reductions higher than 10-20 mmHg, it is recommended to initiate antihypertensive therapy with more than one agent (most patients at high risk will in fact require 2 or more agents to obtain their blood pressure control), as the use of combina-

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tion therapy may allow target pressure achievements in a shorter time and with better outcomes than monotherapy[8].

Hypertension is a multifactorial disorder, in which several biological systems are involved, together with a series of hemodynamic events[11]. Among the different physiological regulation systems, potentially responsible for hypertension development, there are renin-angiotensin-aldosterone system, sympathetic nervous system, natriuretic peptides system, and hormonal system[11]. Alterations of one or more of these systems can contribute to the development and progression of hypertensive disease[11].

The Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a critical role in the pathogenesis of hypertension[3,11]. The RAS is a biochemical complex involved in regulation of several basic biological processes[3,11]. Among the main functions of RAS there are homeostasis of blood pressure, balance of fluid and electrolytes, control of plasma volume, cell growth and regeneration[3,11].

The main effector of RAS is the angiotensin II, an octapeptide produced from its active precursor, angiotensin I, which in turn is formed by the enzymatic action of renin on angiotensinogen[11].

Angiotensin II acts on different target organs (Figure 1), inducing several biological effects highly relevant for hypertension development and for target organ damage (cardiovascular, renal, and cerebral)[3,11]. In particular, angiotensin II plays a defined role in the pathogenesis of left ventricular hypertrophy, stroke, coronary heart disease, and heart failure[1,11].

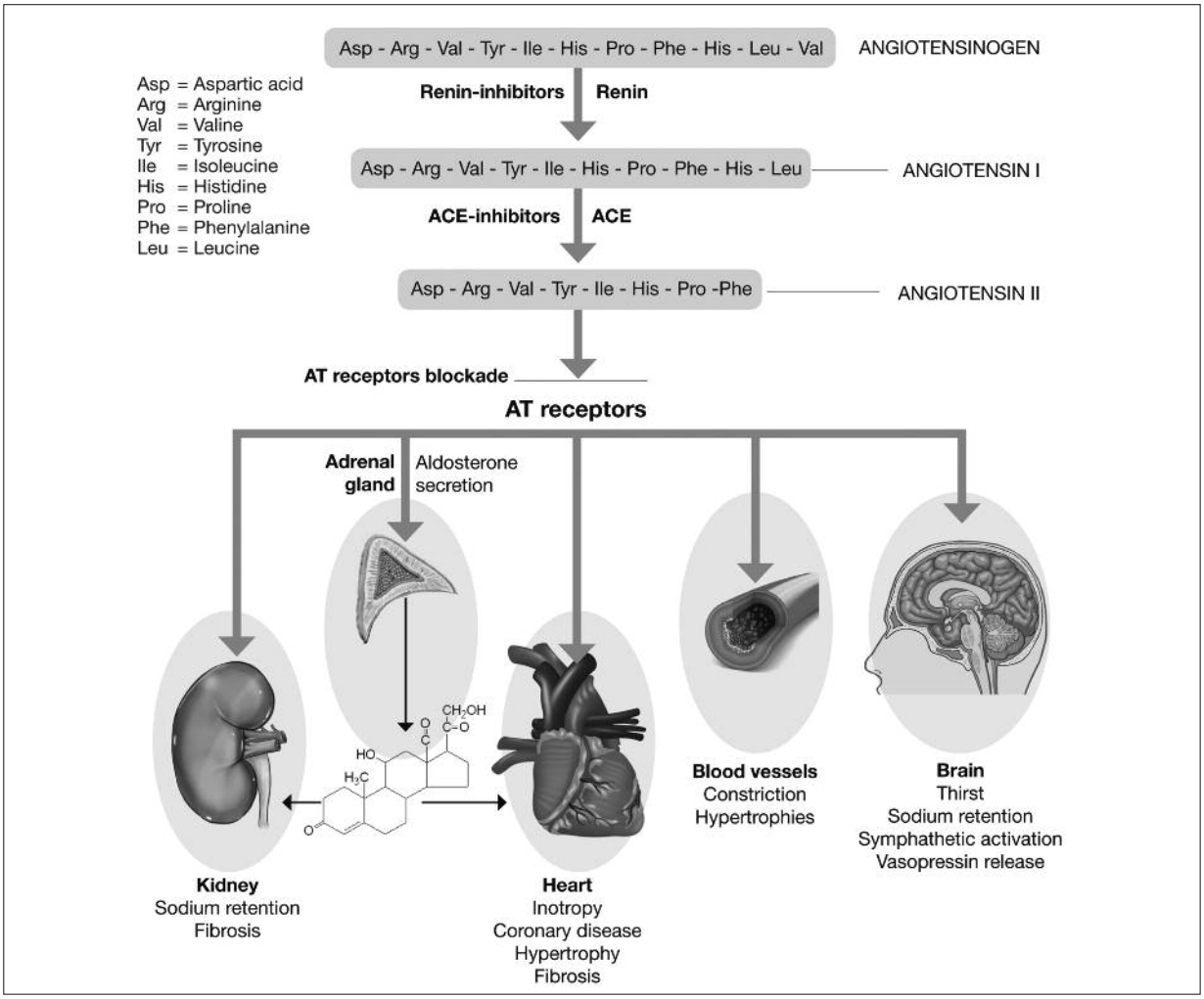

Figure 1. Main target organ of RAS and its most important biological actions in brief. Asp = Aspartic acid; Arg = Arginine; Val = Valine; Tyr = Tyrosine; Ile = Isoleucine; His = Histidine; Pro = Proline; Phe = Phenylalanine; Leu = Leucine. (From Gasbarrini G, mod)[11].

The renin-angiotensin system acts in all parts of the body, with an activity related to that of its limiting enzyme, the renin[11]. Renin is an enzyme released by juxtaglomerular renal cells, linked to aldosterone in a negative feedback loop.

The renin-angiotensin system is involved not only in the mechanisms responsible for hypertension development and cardiovascular damage, but also in the pathogenetic processes conditioning their maintenance, creating a sort of vicious circle[11].

At the end of RAS activation sequence, angiotensin II binds to the receptor subtype AT_1, a specific structure located at cellular level, as indicated in Figure 1[11,12]. Following this binding, a signal is activated and after its intracellular transmission the main biological effects of angiotensin II take place: vasoconstriction, sodium retention, thirst, ADH and aldosterone production, cell growth, fibrosis, proinflammatory, profibrotic, and oxidative activities[11].

The renin-angiotensin system activation can induce development and progression not only of hypertension but also of other severe diseases, as diabetes, atherosclerosis, heart failure, and renal insufficiency[11].

Pharmacological inhibition of RAS can be exerted at 2 levels:

1. Inhibition of angiotensin II synthesis from angiotensin I, through inhibition of angiotensin-converting enzyme (ACE);
2. Block of the angiotensin II receptor AT_1[11,12].

On the first mechanism is based the activity of ACE-inhibitors drugs, the second of the angiotensin-receptor blockers (ARBs)[8,11,12].

The ACE-inhibitors use is associated with an effective blood pressure control and cardiovascular protection, as demonstrated in a great number of clinical studies and in the medical practice during more than 20 years[11,12]. Similarly, ARBs are highly effective as blood pressure control and cardiovascular protection and resulted able to play an important role in diseases other than hypertension, such as heart failure, diabetic nephropathy, and type 2 diabetes[1]. In addition, ARBs are characterised by a better safety profile when compared with ACE-inhibitors. In fact, they are associated to a negligible prevalence of cough, a typical side effect reported with varying frequency in 20-50% of the patients treated with ACE-inhibitors[12-14]. This difference is to be ascribed to the fact that ARBs have no activity on bradykinin metabolism[12].

According to the most recent information on risk factors and cardiovascular damage progression in hypertension, a modern approach to high blood pressure should take in account the achievement of numerous goals, preventing target organ damage at many levels, vascular, cardiac, renal, and cerebral (in particular myocardial infarction, stroke, and heart failure), through an effective antihypertensive treatment, well tolerated and accepted by the patient[11].

Among the various ARBs now available, a particular attention should be paid to valsartan, which in several methodologically adequate studies on large patient populations demonstrated strong antihypertensive efficacy, marked reduction of cardiovascular risks, good safety[1,3,8,15-17], high compliance as well as adherence to therapy by the patients[4,18].

Valsartan: Clinical Profile

Antihypertensive Efficacy

In antihypertensive therapy, valsartan resulted highly effective in several trials in comparison with other active treatments, in monotherapy as well as combination therapy[1,3,8,15-17]. Valsartan was also found particularly active in patients with heart failure and type 2 diabetes[19,20].

Antihypertensive Efficacy in Monotherapy

In a double-blind randomized study, carried out in Japan on 3.081 patients with hypertension and other cardiovascular diseases (Jikei Heart Study)[1], morbidity and mortality has been evaluated in 2 treatment groups:

1. Valsartan 40-160 mg/day;
2. Other antihypertensive drugs, excluding ARBs.

Primary endpoint was a composite of myocardial infarction, admission to hospital (for stroke, TIA, congestive heart failure, and angina pectoris), dissecting aneurysm of the aorta, doubling of serum creatinine, transition to dialysis.

At the end of the study the incidence of primary endpoint was significantly lower in the valsartan group versus comparator: 6% versus 9.7% ($p = 0.0002$).

The primary endpoint frequency in the 2 treatment groups during the 48 months of the study is shown in Figure 2.

The efficacy of long-term treatment with valsartan or amlodipine has been evaluated in more than 15,000 patients in the VALUE Study[15], which ana-

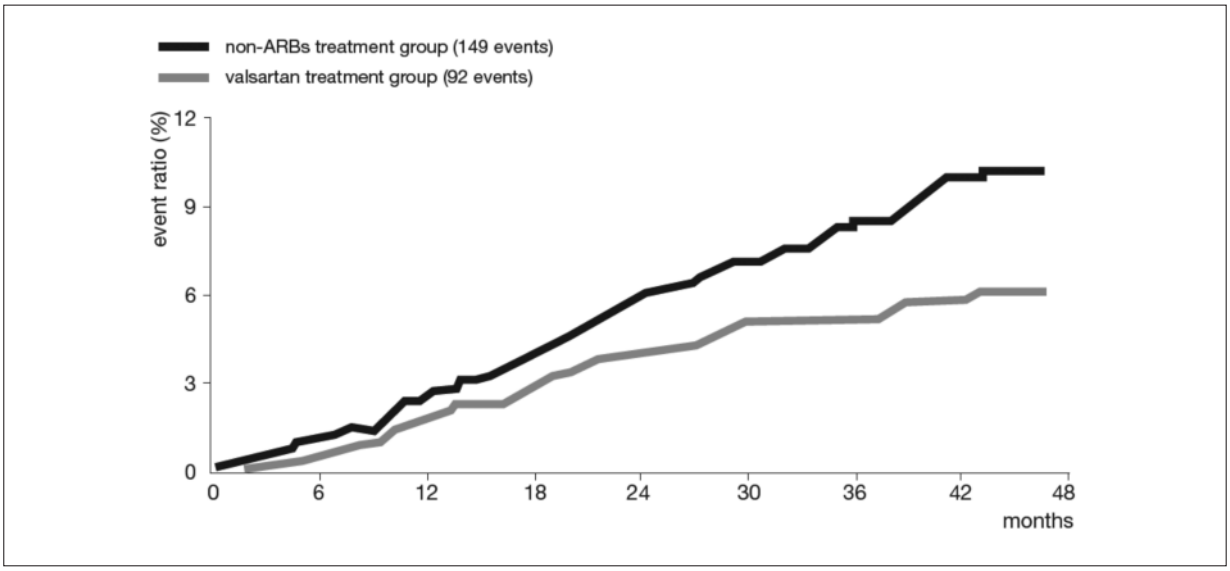

Figure 2. Cumulative frequency of primary endpoint in patients treated with valsartan or other antihypertensive agents: Jikei Study. (From Mochizuki S et al, mod)[1].

lyzed also the results obtained in a subpopulation of 7,080 patients assigned to monotherapy for a 3.2-year period[16].

Incidence of primary endpoint (time to first cardiac event) showed no significant difference between the 2 treatment groups, but the frequency of heart failure was significantly lower in the valsartan group (p = 0.004), a difference amplified by longer duration of monotherapy (Figure 3)[16].

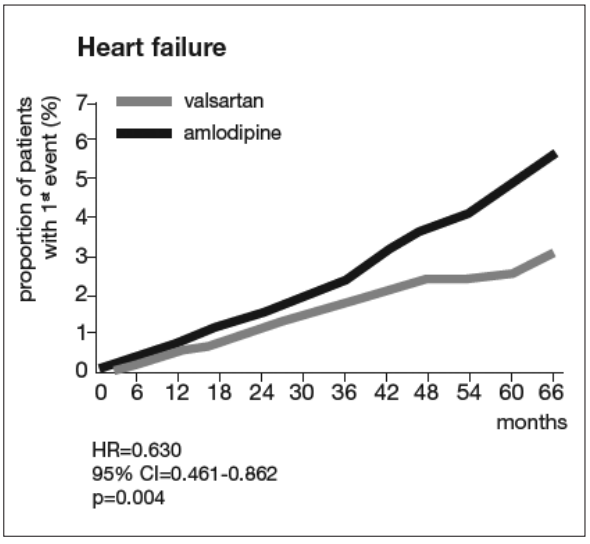

Figure 3. Incidence of heart failure in patients randomized to monotherapy with valsartan or amlodipine: VALUE Study. (From Julius S et al, mod)[16].

Antihypertensive Efficacy in Combination Therapy

In a prospective randomized study on more than 3,000 Japanese patients with uncontrolled hypertension at high cardiovascular risk (Kyoto Heart Study)[3], morbidity and mortality were evaluated in 2 treatment groups:

1. Valsartan add-on therapy: starting from low doses (40-80 mg), to be increased to 160 mg, followed by the combination with other antihypertensive agents, (excluding ACE-inhibitors and ARBs), according to the blood pressure results;
2. Conventional therapy: other antihypertensive agents (excluding ACE-inhibitors and ARBs).

Median follow-up period was of 3.27 years. Efficacy was assessed through a primary endpoint, composite of fatal and non-fatal cardiovascular events.

Patients randomized to valsartan showed a reduced frequency of primary endpoint, significantly lower in comparison with the conventional therapy group (p = 0.00001) (Figure 4).

It must be underlined that even the analysis of the single events included in the primary endpoint showed a series of results favouring valsartan in every case (Figure 5)[3].

For all events the risk estimates favoured valsartan and only for the renal function parameter the same activity was shown[3].

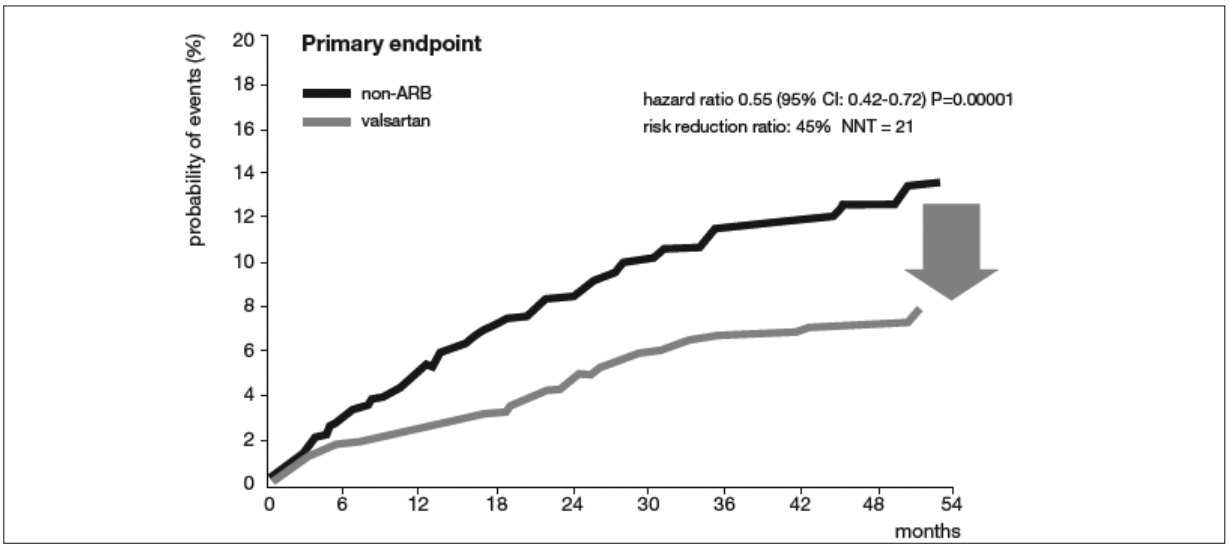

Figure 4. Cumulative frequency of primary endpoint in patients treated with valsartan (add-on therapy) or other antihypertensive agents: KYOTO Study. (From Sawada S et al, mod)[3].

As for valsartan optimal doses, an interesting meta-analysis has been carried out on double-blind randomized placebo-controlled studies, including different dosing schedules in 4,278 patients with grade 1 and 2 hypertension[8]. The objective was to compare the efficacy of increasing doses of valsartan in monotherapy and combination therapy with hydrochlorothiazide (HCT). In addition, time to achieve blood pressure goal was evaluated. Three doses of valsartan were considered (80, 160, and 320 mg), in monotherapy or in association with HCT 12.5 mg.

The results showed that blood pressure control is achieved more frequently and promptly with the higher doses of valsartan, in monotherapy or combined with HCT.

	Valsartan		Non-ARB		Hazard ratio			
	Patients number of events	*/1000 pts. year*	*Patients number of events*	*/1000 pts. year*	*0.25 0.5 1 2*	*HR*	*95% CI*	*P-value*
Primary endpoint	83 (5.5%)	18.7	155 (10.2%)	35.1		0.55	0.4-0.7	0.00001
Acute myocardial infarction	7 (0.5%)	1.6	11 (0.7%)	2.5		0.65	0.2-1.8	0.3947
Angina pectoris	22 (1.5%)	4.9	44 (2.9%)	10.0		0.51	0.3-0.9	0.0106
Heart failure	12 (0.8%)	2.7	26 (1.7%)	5.9		0.65	0.3-1.3	0.2086
Stroke	25 (1.6%)	5.6	46 (3.0%)	10.4		0.55	0.3-0.9	0.0148
Dissecting aneurysm of aorta	3 (0.2%)	0.7	5 (0.3%)	1.1		0.60	0.1-2.5	0.6998
Lower limb arterial obstruction	11 (0.7%)	2.5	12 (0.8%)	2.7		0.99	0.4-2.4	0.9811
Transition to dialysis or doubling of serum creatinine levels	6 (0.4%)	1.3	14 (0.9%)	3.2		0.43	0.2-1.1	0.3467
All cause mortality	22 (1.5%)	4.9	32 (2.1%)	7.2		0.76	0.4-1.3	0.3285
Cardiovascular death	8 (0.5%)	1.8	13 (0.9%)	2.9		0.66	0.3-1.6	0.3712
New onset diabetes	58 (5.2%)	51.6	86 (7.7%)	76.7		0.67	0.5-0.9	0.0282

Figure 5. Hazard ratio estimates for each single event included in the primary endpoint: KYOTO Study. (From Sawada T et al, mod)[3].

The median time to obtain optimal blood pressure control with different valsartan doses is shown in Table I.

The better blood pressure control at higher doses of valsartan in monotherapy and in combination with HCT is shown in Figure 6[8].

The efficacy of valsartan-HCT 25 mg combination has been assessed in comparison with the efficacy of amlodipine-HCT 25 mg combination in 2 groups of 241 patients with blood pressure values of 160-200 mmHg (EVALUATE Study)[17]. Initial doses were of 160 and 5 mg, to be increased up to 320 and 10 mg at the 10th week, respectively for the 2 treatments.

In these high-risk patients it is recommended to start with a combination therapy and the results showed that after 10 weeks of treatment the PAS/PAD reductions from baseline were significantly higher in the valsartan-HCT group than in the amlodipine-HCT group ($p < 0.0001$) (Figure 7).

According to the wide clinical evidence, it can be concluded that valsartan is associated to a high antihypertensive efficacy and to a global cardiovascular protection, both showing superiority in comparison with other antihypertensive agents of proven efficacy.

Safety

In the described clinical studies, valsartan resulted globally comparable as for safety with other antihypertensive agents. Valsartan shows a favourable profile versus amlodipine (the antihypertensive agent most often used as comparator) as well as versus conventional treatments (all other antihypertensive agents excluding ARBs)[1,3,8,16].

In addition, when the studies implied comparisons between different valsartan doses, even in these cases the safety profile was substantially maintained[8].

Table I. Median time to obtain optimal blood pressure control with different valsartan doses.

Valsartan 160 mg	8.1 weeks
Valsartan 320 mg	6.1 weeks
Valsartan 160 mg + HCT	2.6 weeks
Valsartan 320 mg + HCT	2.1 weeks

Adherence to Antihypertensive Drug Therapy

Antihypertensive drug therapy is a chronic therapy and should be maintained indefinitely[4]. However, very frequently in daily clinical practice a low compliance to drug treatment can be found, which strongly hampers the effectiveness of therapeutic measures. In randomized clinical trials the antihypertensive drug discontinuation rates ranged from 5% to 10% per year, but in actual practice rates up to 50-60% after 6 months have been reported.

As known, adherence to antihypertensive drug therapy is associated with improved blood pressure control and better cardiovascular outcomes. For example, it has been demonstrated that a

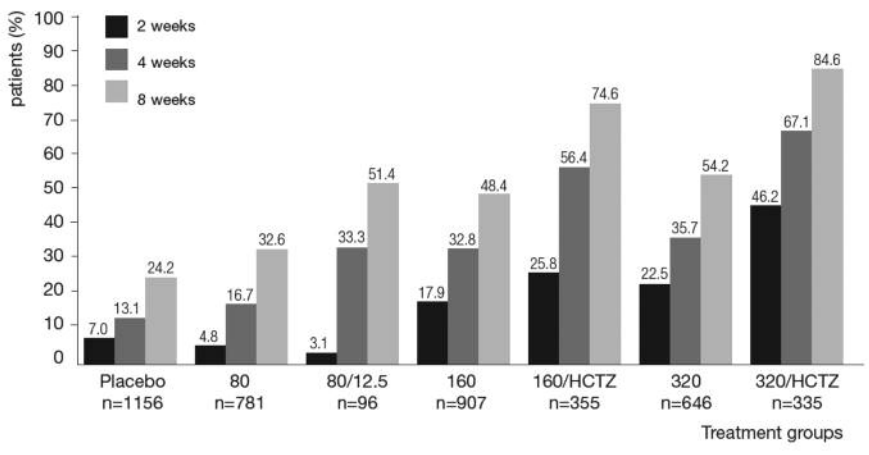

Figure 6. Cumulative proportions of patients achieving the therapeutic goal of PAS/PAD < 140/90 mmHg by 2, 4, and 8 weeks of treatment. (From Weir MR et al, mod)[8].

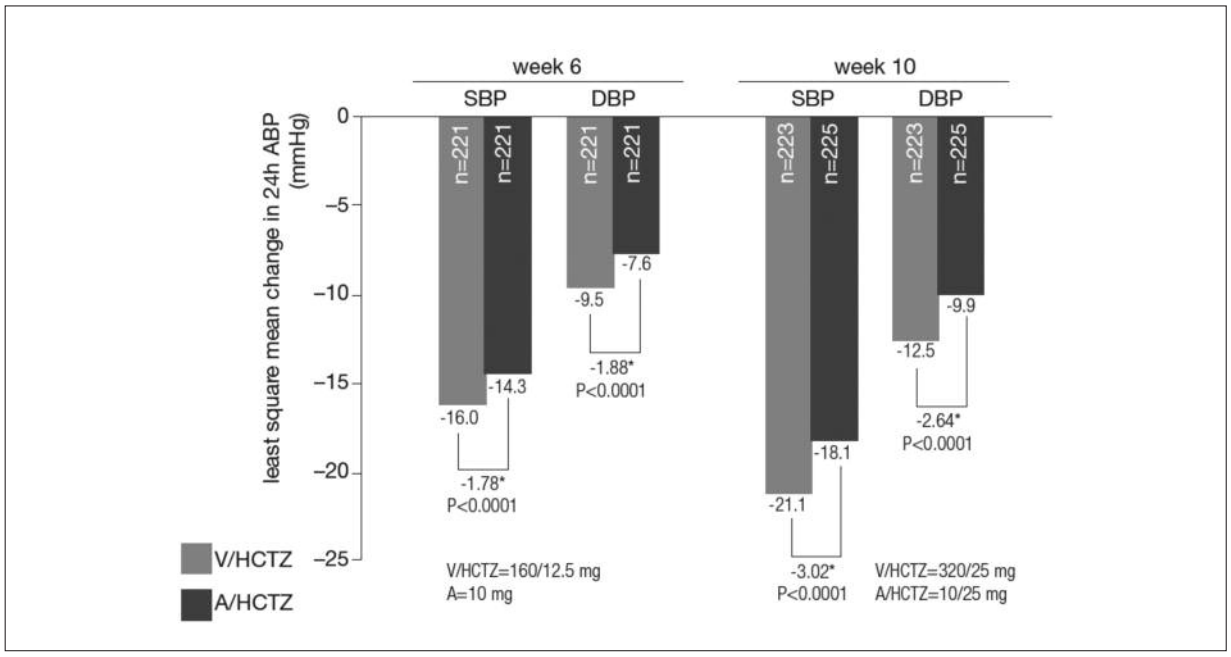

Figure 7. PAS/PAD changes after 6 and 10 weeks of treatment with valsartan-HCT or amlodipine-HCT: EVALUATE Study. ($p < 0.0001$ in favour of valsartan versus amlodipine). (From Lacourciere Y et al, mod)[17].

high adherence to antihypertensive drug therapy after acute myocardial infarction can allow significant long-term survival advantages, positively correlated to pharmacological treatment.

Low compliance to antihypertensive drug therapy and high rates of treatment discontinuation are the causes of inadequate blood pressure control and increased cardiovascular risk[18]. In hypertensive patients having a good compliance to treatment, the stroke incidence can be reduced up to 22%, while non-persistence with antihypertensive drug treatment can be associated with a 28% increase in the risk of stroke and with a 15% increase in the risk of acute myocardial infarction.

In order to assess the impact of nonadherence to antihypertensive drug therapy on the cardiovascular outcomes, a group of Italian Investigators carried out a study on 18,806 newly diagnosed hypertensive patients, using data obtained from 400 primary care physicians providing information to the National Health Authorities during the years 2001-2003[4].

According to the compliance to antihypertensive drug therapy (proportion of days covered by treatment in the mentioned period), patients were classified in 3 groups:

1. High adherence: ≥ 80%;
2. Intermediate adherence: 40-79%;
3. Low adherence: ≤ 40%.

The results showed that only high adherence to antihypertensive drug therapy was associated with a reduced rate of cardiovascular events (–38%, $p = 0.032$ versus low adherence).

The results are similar to those observed in several studies (carried out in UK, Netherlands, and Canada) as well as in recent meta-analyses, which reported a nearly 30% risk reduction of cardiovascular events achieved with different antihypertensive drugs[4].

In addition, not only an effective blood pressure reduction can positively affect cardiovascular outcomes, but also an early and rapid achievement of blood pressure control is associated with benefits for subsequent cardiovascular risk.

Low compliance to antihypertensive drug therapy and high rate of treatment discontinuation are not only the causes of inadequate blood pressure control and higher cardiovascular risk, but also major determinants of increased medical costs[18].

The extent of persistence to antihypertensive drug therapy has been evaluated in an Italian study on 61,493 patients who received their first prescription of antihypertensive medications, as monotherapy or combination therapy (Papeete Study)[18].

Patients were defined "persistent" if 12 months after the beginning of treatment they were still taking a regular therapy (same drug or added one or more drugs or switch to another drug).

Persistence to antihypertensive drug therapy at 12 months was only 11.2%. The most prescribed drugs were ACE-inhibitors (22.8%), beta-blockers (14.3%), diuretics (13.9%), calcium-antagonists (11.4%), and ARBs (9.3%).

The highest level of persistence was observed with ARBs (18.8%).

Pharmacoeconomics Considerations

A non-persistence rate of 88.8% should induce some careful considerations on the seriousness of its possible implications not only clinical, but also economic. In fact, the lack of compliance to therapy, with the subsequent unsuccessful blood pressure control and the associated high risk of cardiovascular events, often imply a more frequent need for hospitalization, one of the major determinant of medical costs[18,21].

A strong support to what stated before is provided by some really impressive USA estimates: according to the American Heart Association, in 2005 about 71% of hypertensive patients had suboptimal blood pressure control, which resulted in 39,702 cardiovascular events and 8,374 deaths, for a total medical expenditure of 964 millions of US dollars[18]. In Europe it has been estimated that if hypertension management achieved blood pressure targets, it could be saved up to 1.26 billions of euros[22].

A marked improvement in blood pressure control, which was registered in UK between 2003 and 2006, was associated with changes in prescription habits, progressively favouring ACE-inhibitors and ARBs, instead of diuretics and beta-blockers[23].

Undoubtedly, when compared with older antihypertensive agents, ARBs can imply a higher cost for drug acquisition, but the evaluation of their impact on medical expenditure must take in account the higher efficacy and the better adherence to therapy by the patients.

ARBs, thanks to the high level of effectiveness and adherence/persistence, provide a favourable impact on health costs[18].

Proper studies in this sense evidenced among ARBs some differences between various agents, as for persistence to treatment, suggesting a better profile for valsartan[18].

As for Italy, in a speculative sense, lacking a cost analysis at national level, the higher adherence to therapy observed with valsartan could represent an important requisite for a positive impact on health costs, whose control is today an absolute priority in Italy and in many other Countries worldwide.

Conclusions

The evidence found in Europe and USA should induce to a careful evaluation of cost-benefit and cost-effectiveness ratios of molecules as valsartan, characterized by a widely documented clinical activity and by a marked adherence by the patients to its use.

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