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Review article

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BLOCKING OF RENIN-ANGIOTENSIN -ALDOSTERONE SYSTEM: MESSAGE FROM LARGE CLINICAL STUDIES

SUMMARY

Hypertension is one of the most common worldwide diseases afflicting humans. Multiple factors modulate the blood pressure for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. These changes can lead to the development of left ventricular hypertrophy, systolic and diastolic LV dysfunction, coronary artery disease, cardiac arrhythmias and heart failure. A lot of studies such as HOPE, EUROPA, VALUE, RESOLVD, LIFE, in the last 20 years tested the effects of angiotensin converting enzyme inhibitors and angiotensin-1-receptor blokers in patients with hypertension associated with left ventricular hypertrophy, and coronary disease. Both angiotensin-converting enzyme inhibitors and angiotensin-1-receptor blokers, effectively inhibit the renin-angiotensin-aldosterone system, but they do so by affecting different parts of the cascade. Several angiotensin-1-receptor blokers (losartan, valsartan, candesartan) have shown to be similarly potent when compared to angiotensin converting enzyme inhibitors in reducing mortality in heart failure patients as well as after acute myocardial infarction; this has been proven in several trials, such as ELITE II, VALHEFT, CHARM and ONTARGET. Nowadays, with the aim to achieve the total blockage of renin-angiotensin-aldosterone system, a new group of drugs aldosterone receptor antagonist is used.

Key words: **arterial hypertension, left ventricular hypertrophy, heart failure, angiotensin-converting enzyme inhibitors, angiotensin-1-receptor blokers**

INTRODUCTION

Hypertension is one of the most common worldwide diseases afflicting humans. At the beginning of a new millennium, more than 50% of people, 65 years of age or older, suffer from arterial hypertension. The estimated total number of adults with hypertension in 2000 was 972 million, and the number of adults with hypertension in 2025 was predicted to increase by about 60% of the total world population (1) *(Figure 1)*. According to the frequency of physician visits, arterial hypertension occupies the first place among all chronic diseases.

The aim of the treatment of arterial hypertension is to decrease the risk of cardiovascular morbidity and mortality by reducing the blood pressure (BP) to the level less than 140/90mmHg. Elevated BP leads to adverse changes in cardiac structure, and function in two ways: directly by increased afterload and indirectly by associated neurohormonal and vascular changes. Multiple factors modulate the blood pressure for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume,

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vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. These changes can lead to the development of left ventricular hypertrophy (LVH), systolic and diastolic LV dysfunction, coronary artery disease, cardiac arrhythmias and heart failure (2)

There are two main types of angiotensin II receptor: AT1 and AT2. Most actions of angiotensin II are mediated through the AT1 receptor (3).

According to European guidelines for the management of arterial hypertension European Society of Hypertension and European Society of

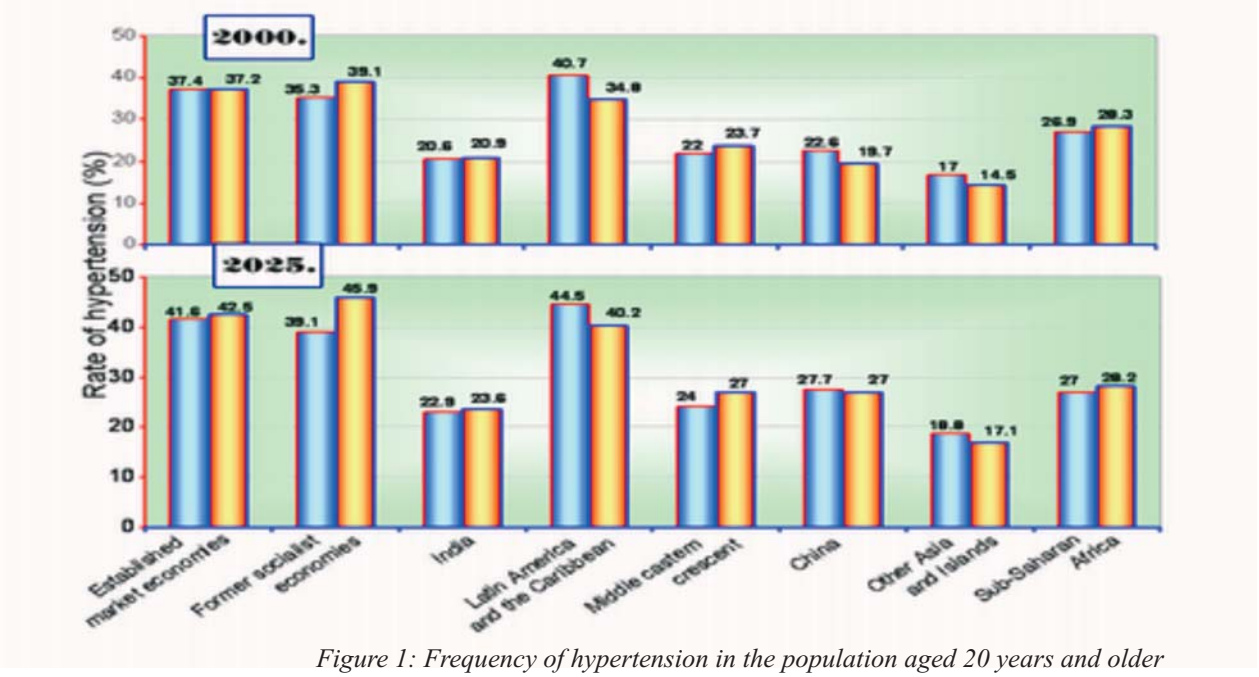

Figure 1: Frequency of hypertension in the population aged 20 years and older by world region and sex in 2000 (upper) and 2025 (lower)

Left ventricular hypertrophy in patients with hypertension is associated with an increased risk for many cardiovascular events and it is an independent risk factor for mortality including sudden cardiac death. In hypertension, LVH is initially a useful compensatory process that represents an adaptation to increased ventricular wall stress; however, it is also the first step toward the development of overt clinical disease. Distension of cardial myocytes is the result of their permanent chronic volume or pressure overload and accumulation of fibroblasts and collagen type I. The left ventricular diastolic function is markedly compromised in long-standing hypertension. In addition to the hemodynamic burden (pressure or volume overload) and demographic factors, several trophic humoral factors, such as angiotensin II, aldosterone, endothelin, leptin, and catecholamines, may also contribute to the development and progression of LVH (2).

Angiotensin II is an important mediator in the human body, which is synthesized in several steps. Its main action is vasoconstriction, but angiotensin II stimulates the proliferation of cells including vascular smooth muscle cells and cardiac myocytes. Thus, an enhanced activity of the RAS leads to a remodeling of blood vessels with increased intimal thickening and ventricular hypertrophy. Cardiology (2007), there are five major classes of antihypertensive agents: diuretics, beta-blockers, calcium antagonists, Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARB) (4).

ACE-inhibitors and ARB are potent inhibitors of LVH. ARB specifically block the angiotensin II receptor AT1, and this causes blockade of the renin-angiotensin aldosterone system (RAAS), including the proliferation of vascular smooth muscle cells by selective binding to the AT1-receptor, though the blockade RAAS is not complete. Because angiotensin can be synthesized outside the renin-angiotensin system, ARB could produce more effective control of angiotensin II than ACE inhibitors. Angiotensin I can be converted to angiotensin II in the heart by enzymes such as cathepsin, trypsin, and heart chymase, but the exact contribution of these alternative pathways to the generation of angiotensin II is unclear.

Angiotensin II blockade causes an increased flux of superoxide that improves NO bioactivity. Most important, AT2 receptors are not blocked by ARB. It appears that AT2 receptors mediate a physiologic cardioprotective role: production of bradykinin, NO, prostaglandins in the kidney, inhibition of cell growth, promotion of cell differentiation, and apoptosis (3).

Both ACE inhibitors and ARB effectively inhibit the renin-angiotensin-aldosterone system, but they do so by affecting different parts of the cascade. The ARB specifically block only the AT1 receptor and allow the AT2 receptor to be stimulated by circulating angiotensin II. ACE regulates the balance between the vasodilative and natriuretic properties of bradykinin and the vasoconstrictive and salt-retaining properties of angiotensin II. The ACE inhibitors effectively block the conversion of angiotensin I to angiotensin II, but by doing so, they also stop the conversion of bradykinin, tachykinin, substance P, and perhaps other important proteins of this type into inactive products. Many authors confirm that bradykinin contributes to the short-term lowering of blood pressure seen after ACE inhibition. As ARB does not interfere with the bradykinin pathway, one might presume that ACE inhibitors would be more powerful antihypertensive agents than ARB. Overall differences between ARB and ACE inhibitors have not been noted in clinical trials (3,5).

The effects on LV fibrosis were attributed to inhibition of collagen synthesis rather than to enhancement of collagen degradation and were likely to result in the attenuation of myocardial stiffness. The combination therapy with ARB and ACE-inhibitors blocked the progression of ventricular fibrosis and hypertrophy, even without reduction in blood pressure (6).

A lot of studies in the last 20 years tested the effects ACE-inhibitors and ARB in patients with hypertension associated with LVH and coronary disease (7-10).

The Heart Outcomes Prevention Evaluation Study (HOPE) showed that in a high-risk group of 9.540 patients (81% ischemic heart disease, 11% stroke, 38% diabetes), 10 mg of ramipril given for a mean of 4.5 years compared to the placebo group caused a reduction of 22% in the primary outcome of MI, stroke, or cardiovascular death.

In the HOPE trial in patients with high cardiovascular risk (mostly because of a history of myocardial infarction) and thus multiple drug treatment, administration of ramipril caused a modest blood pressure reduction (about 3 mmHg systolic blood pressure) and a clearcut reduction (-22%) in the incidence of cardiovascular events compared to the placebo group (7,8).

In the EURopean trial on reduction of cardiac events, with Perindopril in stable coronary artery disease investigators (EUROPA) trial, in patients with coronary disease (and thus multiple background treatmen), blood pressure lowering (-5/-2 mmHg) by an ACE inhibitor (perindopril with the possible addition of indapamide) was accompanied by beneficial cardiovascular effects compared with placebo, independent of the baseline blood pressure value. There was a 20% relative risk reduction for primary endpoint (cardiovascular death, myocardial infarction or cardiac arrest) (9).

The Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) addressed the role of ARB (valsartan) compared to the calcium channel blocker (amlodipine) in high-risk 15.245 hypertensive patients. In this trial, there were no differences in reducing cardiovascular events between the treatment groups with Valsartan (10.6%) and Amlopidine (10.4%) (10).

The Randomised Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial was the first clinical trial to address the beneficial effects of adding ARB to ACEI therapy. Four hundred and twenty-six of 768 patients receiving candesartan, enalapril or combination were randomized to either metoprolol or placebo. Patients were New York Heart Association class II–IV, ejection fraction (EF) <0.40 and 6-min walk distance <500m. The primary endpoint in this trial was remodeling of LV. These data demonstrated that the combination of candesartan and enalapril was more effective than either therapy alone in retarding progressive structural change. Blood pressure decreased with combination therapy compared with candesartan or enalapril alone (P<0.05). End-diastolic (EDV) and end-systolic (ESV) volumes increased less with combination therapy (EDV 8±4 mL; ESV 1±4 mL; P<0.01) than with candesartan alone (EDV 27±4 mL; ESV 18±3 mL) or enalapril alone (EDV 23±7 mL; ESV 14±6 mL) (11).

In the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) in more than 9.000 hypertensive patients with electrocardiographic left ventricular hypertrophy mean blood pressure was reduced to the same degree in the groups in which treatment was initiated with either losartan or the b-blocker (atenolol). Over about five years of follow-up losartan-treated patients showed a significant (13%) reduction in major cardiovascular events (the primary end point) with no difference in the incidence of myocardial infarction, but a 25% difference in the incidence of stroke (12).

A meta-analysis of five trials which assessed the effects of treatment on left ventricular mass in essential hypertension showed that left ventricular mass index was decreased by ARB 13%, Calcium channel blockers 11%, ACE-inhibitors 10%, diuretics 8%, veta blockers 6% (13) *(Figure 2)*.

Arterial hypertension caused LVH which developed diastolic and systolic left ventricular dysfunction. In hypertensive disease, damage of coronary microcirculation can be pathological-anatomical basis in reducing coronary reserve with

clinical signs of myocardial ishemia and further development of heart failure. Heart failure affects 2% of the population in the developed world, and the absolute number of people living with the syndrome is set to increase steeply in the next decades because of an improving prognosis and a rapidly aging population (14,15).

The most important reason that the ELITE study results were different from those of much larger ELITE II study was that ELITE was too small and thereby underpowered. Furthermore, the ELITE primary end point was not mortality but renal insufficiency development (16).

The Valsartan Heart Failure Trial (Val-HeFT) study is the largest trial to date where ARB

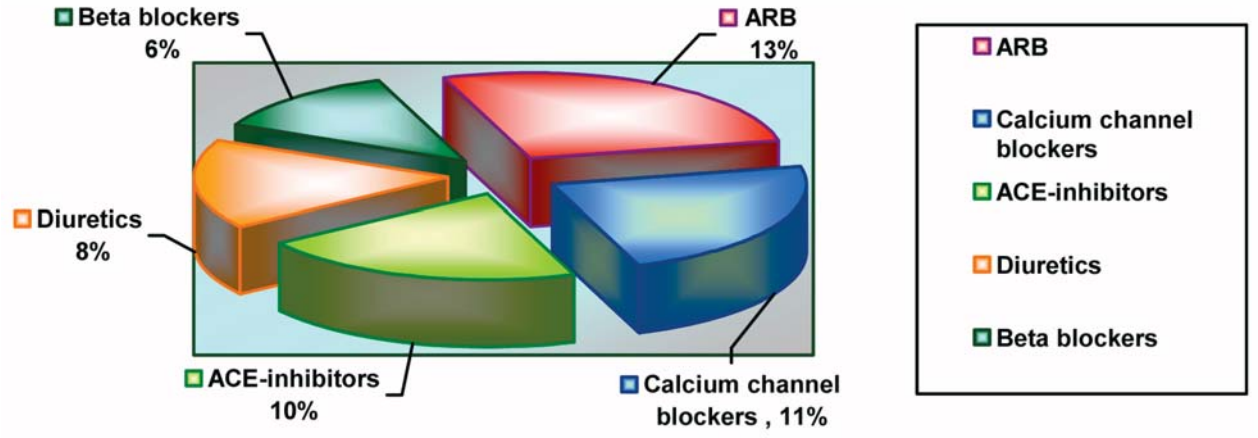

Figure 2. Meta-analysis of the effects of treatment on left ventricular mass in essential hypertension

Several ARB (losartan, valsartan, candesartan) have shown to be similarly potent when compared to ACE-inhibitors in reducing mortality in heart failure patients as well as after acute myocardial infarction; this has been proven in several trials; ELITE II, VALHEFT, and CHARM.

The ELITE (Losartan Heart Failure Survival Study) compared the effect of the classic ACE inhibitor captopril and AT1 receptor antagonist losartan in 3.152 patients over 65 with mild HF due to systolic dysfunction. Losartan was found to be superior to captopril with a mortality reduction and better tolerance. The apparent advantage of losartan was almost exclusively due to a reduction of sudden death. After these exciting findings, the outcome of ELITE II, a sequel to the ELITE study, which did not show additional protection of losartan compared to captopril, was disappointing. There was not a significant difference in mortality reduction with both drugs *(Table 1)*.

therapy has been added to standard neurohormonal blockade in systolic dysfunction heart failure. This study is the first to demonstrate a mortality benefit for ARB therapy when prescribed to ACEI-intolerant patients not on beta blockade. These study was randomized involving 5.010 patients, aged ≥ 18 years, with ejection fraction < 40% and left ventricular dilatation. The AT1 receptor blocker valsartan added to conventional treatment (ACE inhibitors in 93%, ß-blockers in 35%, and spironolactone in 5% of patients) produced a significant reduction in cardiovascular morbidity that was primarily (13.2%) the result of a 24% reduction in first HF hospital admissions, although the all cause mortality remained unaffected (17).

The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) study programme was specifically designed as three parallel, independent, integrated,

Table 1. Results of ELITE-II

End point	Captopril (n=1574)	Losartan (n=1578)	Risk ratio	95% CI	*P*
All-cause mortality	15.9%	17.7%	0.88	0.75-1.05	0.16
Sudden death/resuscitated cardiac arrest	7.3%	9.0%	0.80	0.63-1.03	0.08
All-cause mortality/ hospitalizations	44.9%	47.7%	0.94	0.85-1.04	0.21
Withdrawal rate	14.5%	9.4%	-	-	0.001

clinical trials comparing candesartan with placebo in three distinct but complementary populations: those with left ventricular ejection fraction (LVEF) ≤ 40% treated with an ACE inhibitor (CHARM-Added, n=2548), those with LVEF ≤ 40% but intolerant of ACE inhibitors (CHARM-Alternative, n=2028), and those with LVEF > 40% (CHARM-Preserved, n=3025).

greater reduction) and the combination-therapy group (a 2.4/1.4-mm-Hg-greater reduction) than in the ramipril group. At the end of the study, the primary end point (a composite of cardiovascular death, MI, stroke, or hospitalization for HF) and changes in left ventricular mass by treatment had occurred in a similar number of patients in all three groups of patients *(Table 2)*.

Table 2. Results of ONTARGET

Outcome	Ramipril n=8576(%)	Telmisartan n=8542(%)	Combination n=8502 (%)	Risk ratio (95% CI), telmisartan vs ramipril	Risk ratio (95% CI), combination therapy vs ramipril
CV death/MI/stroke/ CHF hospitalization[a]	16.5	16.7	16.3	1.01 (0.94 - 1.09)	0.99 (0.92 - 1.07)
MI	4.8	5.2	5.2	1.07 (0.94 - 1.22)	1.08 (0.94 - 1.23)
Stroke	4.7	4.3	4.4	0.91 (0.79 - 1.05)	0.93 (0.81 - 1.07)
CHF hospitalization	4.1	4.6	3.9	1.12 (0.97 - 1.29)	0.95 (0.82 - 1.10)
CV death	7.0	7.0	7.3	1.00 (0.89 - 1.12)	1.04 (0.93 - 1.17)
Any death	11.8	11.6	12.5	0.98 (0.90 - 1.07)	1.07 (0.98 - 1.16)
Renal impairment	10.2	10.6	13.5	1.04 (0.96 - 1.14)	1.33 (1.22 - 1.44)

[a] *Primary end point*

The overall CHARM program (n=7601) was a separately powered and analyzed cohort comprising the 3 CHARM clinical trials with the overarching end point of total mortality, irrespective of background therapy or baseline LVEF. This design feature was carefully considered and important because earlier studies with ACE inhibitors, ß-blockers, aldosterone antagonists, and ARB in HF were conducted specifically in this problematic population. Cardiovascular deaths were fewer in the candesartan group (35.7%) than in the placebo group (41.3%). Candesartan also significantly reduced the total number of CHF hospitalizations by 27%.

The results of CHARM additional prespecified analyses from the CHARM program demonstrate that the ARB (candesartan) significantly reduced cardiovascular death, hospital admission for decompensated heart failure, and all-cause mortality in patients with CHF and LVEF <when added to standard therapies including ACE inhibitors, ß-blockers, and an aldosterone antagonist, or their combination (18).

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial (ONTARGET) enrolled 25.620 patients with coronary heart disease or diabetes plus additional risk factors who were over the age of 55 years but with evidence of heart failure. Patients were randomized to receive ramipril 10 mg per day, telmisartan 80 mg per day, or the combination of the two. The mean duration of follow-up of the study was 55 months.

Results showed that mean blood pressure was lower in the telmisartan (a 0.9/0.6-mm-Hg-

Compared with the ramipril group, telmisartan patients had lower rates of cough and angioedema and a higher rate of hypotensive symptoms (19,20).

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) randomized 14.703 patients with heart failure and/or left ventricular ejection fraction <40% to receive captopril, valsartan, or both. In the VALIANT study like ONTARGET, the combination therapy with valsartan and captopril was equivalent to captoprol monotherapy for preveting cardiovascular mortality and morbidity in patients with acute MI accompanied by left ventricular dysfunction or heart failure. There was no difference in outcomes (cardiovascular mortality, MI, heart failure, resuscitated arrest, or stroke) between treatment groups with valsartan, captopril and both. Combining valsartan with captopril increased the rate of adverse events without improving survival. In VALIANT, elderly patients had good compliance with the study medications but received lower doses of captopril, valsartan, and combination therapy than younger patients did. In the doses used, captopril and valsartan achieved similar outcomes in elderly patients. During a median follow-up of 24.7 months, mortality from any cause was 19.9% in the valsartan group, 19.5 % in the captopril group and 19.3 % in the valsartan and captopril group (21).

Nowadays, a new group of drugs-aldosterone receptor antagonists are used with purpose of total RASS blocking. Mechanism of action of these drugs is competitive binding to the cell receptors in renal tubule which prevent the disabled aldosterone to bind. Also, aldosterone-receptor antagonists may

prove benefit which includes prevention of remodeling and fibrosis, improvement of hemodynamics and prevention of sudden cardiac death (22-24).

4E (Effects of Eplerenone, Enalapril and Eplerenone/Enalapril)-Left Ventricular Hypertrophy study included 202 hypertensive patients with left ventricular hypertrophy. The primary end point in the trial was a change in left ventricular mass as assessed by magnetic resonance imaging. The results from serial magnetic resonance imaging evaluation demonstrated a significant reduction (27gr) over a 9-month period in left ventricular mass in the group treated with eplerenone/enalapril compared with the eplerenone monotherapy group (22).

Two large trials have evaluated the use of an aldosterone receptor antagonist in patients with heart failure in addition to an ACE inhibitor: the Randomized Aldactone Evaluation Study (RALES) study and the Eplerenone Heart Failure Efficacy and Survival Study (EPHESUS).

In the RALES study, there was a 30% reduction in mortality among patients with chronic moderate to severe heart failure randomized to spironolactone (NYHA class III,IV), together with a reduction in frequency of hospitalization for worsening heart failure. In the EPHESUS study, the selective aldosterone receptor antagonist eplerenone was administered within 3–14 days of MI (i.e. during the acute phase) to patients with LVEF < 40%, most of whom had symptoms of heart failure (NYHA class II-IV). At mean follow-up of 16 months, there were 15% significant reductions in all-cause mortality, cardiovascular disease and hospitalisation with Eplerenone in addition to standard therapy (23,24).

CONCLUSION

This review of large studies showed that angiotensin-converting enzyme inhibitors, angiotensin-1-receptor blokers and aldosterone receptor antagonist within the aim of total blockage of the renin-angiotensin aldosterone system reduced LVH, lower the incidence of cardiovascular morbidity and mortality, and hospitalization in patients with arterial hypertension and patients with heart failure.

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BLOKADA RENIN-ANGIOTENZIN-ALDOSTERON SISTEMA: PORUKA VELIKH KLINIČKIH STUDIJA

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SAŽETAK

Hipertenzija je jedna od najčešćih bolesti u svetu koja pogađa ljudsku populaciju. Mnogobrojni faktori modifikuju krvni pritisak obezbeđujući adekvatnu perfuziju tkiva i oni obuhvataju humoralne medijatore, vaskularnu reaktivnost, cirkulišući krvni volumen, viskoznost krvi, promer krvnih sudova, kardijalni minutni volumen, elastičnost krvnih sudova i neuralnu stimulaciju. Ove promene mogu voditi ka razvoju hipertrofije leve komore, sistolne i dijastolne disfukcije leve komore, koronarne bolesti, srčanih aritmija i srčane insuficijencije. Tokom poslednjih dvadeset godina, brojne studije, kao što su HOPE, EUROPA, VALUE, RESOLVD, LIFE, proučavale su efekte inhibitora konvertujućeg enzima i inhibitora angiotenzin -1 receptora kod hipertenzivnih bolesnika sa hipertrofijom leve komore i koronarnom bolešću. Inhibitori konvertujućeg enzima i inhibitori angiotenzin -1 receptora blokiraju renin-angiotenzin-aldosteron sistem, ali na različitim nivoima kaskade. Nekoliko inhibitora angiotenzin -1 receptora (losartan, valsartan, candesartan) pokazuju sličnu efikasnost u poređenju sa inhibitorima konvertujućeg enzima u redukciji mortaliteta kod bolesnika sa srčanom insuficijencijom, kao i nakon preživelog infarkta miokarda. Ovo je dokazano u nekoliko studija ELITE II, VALHEFT CHARM i ONTARGET. U cilju kompletne blokade renin-angitenzin-aldosteron sistema danas je u upotrebi nova grupa lekova-antagonisti aldosteron receptora.

Ključne reči: **arterijska hipertenzija, hipertrofija leve komore, srčana insuficijencija, inhibitori konvertujućeg enzima, blokatori angiotenzinskih 1-receptora**