Renin-angiotensin system blockade in the treatment of heart failure and the role of valsartan in this treatment

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ABSTRACT

Heart failure which occurs due to various causes including primarily coronary artery diseases and hypertension is a syndrome with complex physiopathology and clinic that can impair patients' quality of life or lead to death. However, it is well known that the activation of renin-angiotensin system (RAS) has an important role in the physiopathology of heart failure with reduced ejection fraction. Therefore, suppression of this system for achieving a gain in the treatment of the disease has been among prominent concerns. In this review, the place of RAS suppressive drugs and valsartan, which is an angiotensin receptor blocker, in heart failure will be examined. *(Anadolu Kardiyol Derg 2014; 14(Suppl 2): S1-S8)*

Key words: heart failure, angiotensin receptor blockers, valsartan

Introduction

Heart failure (HF) is a complex syndrome that occurs when the filling and ejection of the blood by the ventricle is limited. This is due to any functional or structural disorder of the ventricle (1, 2). This syndrome, caused by valve diseases, congenital heart diseases, pericardial diseases, primary diseases of the myocardium, some metabolic disorders, and most frequently coronary artery diseases and systemic hypertension, restricts people's lives, leads to frequent hospitalization, or death. It is evident that the purpose of the treatment of this condition is to get rid of these limiting and destructive effects.

The current treatment of this disease is determined according to the left ventricular ejection fraction. HF with preserved (unimpaired) ejection fraction is one condition that differs in its pathophysiology and there is almost no evidence that medical therapy can decrease mortality and hospitalizations (3). On the other hand, HF with reduced ejection fraction (HFrEF) is a condition that has been studied in more detail; its pathophysiology especially the role of neuro-humoral mechanisms are well established, and the benefits of medical therapies on survival are proven by randomized controlled trials (RCTs) (4). In this review, the role of renin-angiotensin system (RAS) in HFrEF, the benefits of the suppression of RAS activation, and valsartan as an angiotensin receptor blocker (ARB) in the treatment of HFrEF are discussed.

The renin-angiotensin-aldosterone system in pathophysiology of Heart Failure
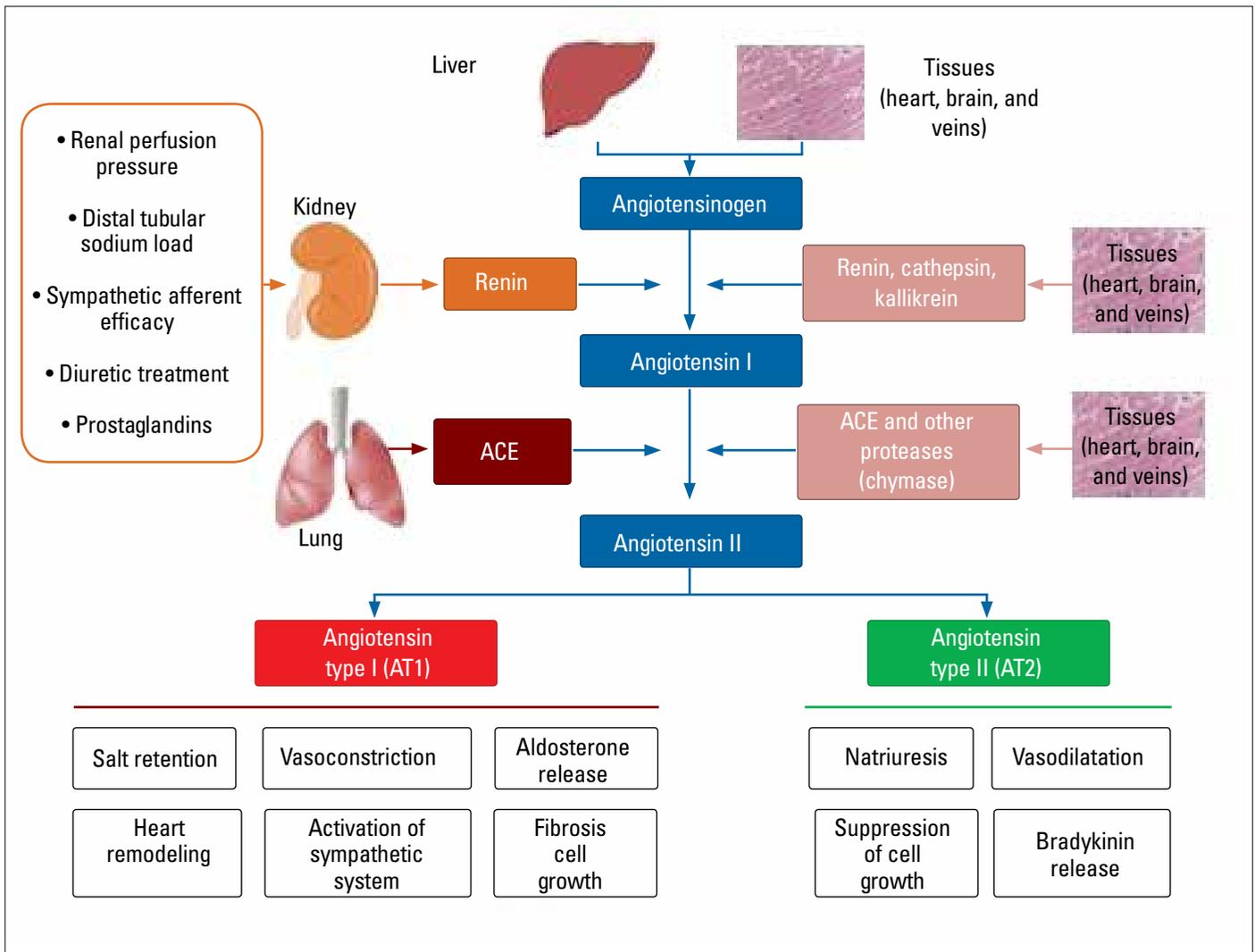
The adrenergic nervous system and renin-angiotensin-aldosterone system (RAAS) are activated as compansating mechanisms in HF. In the early phase of the disease RAAS activation increases water and salt retention, leads to vasoconstriction in peripheral arteries, temporarily improves myocardial contractility, and contributes to the cardiac repair process, thus keeping cardiac output within the normal limits. However, if the activation is chronic, overproduction of some biomolecules with destructive effects on the cardiovascular system takes place. These molecules cause remodeling of the heart and progression and deterioration of HF. Heart failure is characterized with a high level of renin which is released from the juxtaglomerular apparatus as a result of reduction in renal blood flow and the stimulation of sympathetic tone (Fig. 1). Renin converts the circulating angiotensinogen synthesized in tissues and the liver into angiotensin I, which is a biologically inactive molecule. The angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, which is biologically active. Although ten percent of ACE activity takes place in the cardiac interstitium and blood vessel

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Figure 1. Activation of renin-angiotensin-aldosterone system
ACE - angiotensin converting enzyme

walls the remaining 90% takes place in other tissues(4). The conversion of angiotensinogen to angiotensin I is also catalyzed by enzymes such as kallikrein and cathepsin G, apart from renin (Fig. 1). Similarly, angiotensin I can also be converted to angiotensin II by chymase activation. Angiotensinogen and ACE, mRNA levels are reported to be increased in patients developing HF and this is independent from the etiology (5). The chymase pathway is considered to play an important role in the formation of angiotensin II in the myocardium especially in patients in whom renin and angiotensin I levels are increased due to chronic administration of ACE inhibitors (ACE-I) (6).

Angiotensin exerts its effects by binding to two receptors, namely angiotensin type 1 (AT1) and angiotensin type 2 (AT2). AT1 receptor is predominantly found in vessels. Although both AT1 and AT2 receptors are found in the heart tissue, the dominant receptor type of the myocardium is AT2. Activation of AT1 receptors causes vasoconstriction, cell growth, release of aldosterone, and catecholamine secretion, whereas stimula-

tion of AT2 receptors leads to vasodilatation, suppression of cell growth, natriuresis, and bradykinin secretion. The negative molecular and structural changes caused by angiotensin II in the heart are considered to be conducted through AT1 receptors. The density of AT2 receptors was reported to be increased in proportion to AT1 receptors in patients with HF (7). Secretion of a high level of angiotensin II for a long time in cases with HF leads to the heart muscle cell hypertrophy independent of its hypertensive effect. The effects on the cardiac muscles are not limited to the heart muscle cell hypertrophy. Secretion of high levels of angiotensin II also causes hypertrophy of fibroblasts and accumulation of collagen in interstitial tissues. The inevitable outcome of these changes is fibrosis. In addition to stimulating the proliferation of fibrosis directly, angiotensin II accelerates this process indirectly via increasing the release of norepinephrine from the sympathetic nerve endings and aldosterone from the suprarenal glands. Its effect on the level of aldosterone is not only limited to the suprarenal gland. The

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Table 1. ACE-I in patients with heart failure

	CONSENSUS	SOLVD-T	SOLVD-P	V-HeFT II	ATLAS
Number of patients	253	2569	4228	806 male	3164
Functional capacity (NYHA)	IV	II-III	Asymptomatic	II-III	II-IV
Molecule	Enalapril vs. Placebo	Enalapril vs. Placebo	Enalapril vs. Placebo	Enalapril vs. Hydralazine + ISD	Low-dose (2.5-5 mg) x high-dose (32.5-35 mg) lisinopril
LVEF, %	Not a criterion for involvement in the study	≤35	≤35	≤45	≤30
Mean duration of follow-up	188 days	3.5 years	3.1 years	2.5 years	3.8 years
Significant risk reduction, %					
Mortality	40% in 6 months, 31% in a year	16%	No difference	28%	No difference
Other	Mortality from progressive HF	Mortality and hospitalization for HF 26%	Mortality and hospitalization for HF 20% / Hospitalization for HF 44% / Development of symptomatic HF 37%		Mortality and hospitalization for any reason 12% / Hospitalization for HF 24%

ISD - isosorbide dinitrate; HF - heart failure; LVEF - left ventricle ejection fraction

increase of the number of aldosterone receptors in the cardiac muscle in subjects with HF suggests that angiotensin II also accelerates the production of aldosterone locally (8). It is known that exposure to high levels of aldosterone for a prolonged time triggers cardiac muscle hypertrophy, fibrosis, and collagen accumulation. If this fibrotic process is not halted, enlargement of the left ventricular cavity, systolic dysfunction, deterioration of HF, and death are inevitable. Therefore, therapies focusing on suppression of RAS plays a central role in management of patients with HF.

ACE-inhibitors in the treatment of heart failure

As emphasized in the introduction, the main purpose of HF treatment is to improve the symptoms, reduce hospitalization, and decrease mortality. The clinical outcomes stated above are also primary endpoints of RCTs that have investigated drug impact in HF. The effects of ACE-I, which were the first drugs developed to suppress RAS activity, were tested in HF patients with placebo controlled RCTs. Before reviewing the results of clinical studies, it is useful to recall the effects of ACE-I on RAS. AT2 production is blocked with ACE inhibition. At the same time, this inhibition decreases kininase II enzyme activity leading to a reduced degradation of bradykinin Increased levels of bradykinin stimulates the production and secretion of nitric oxide and protacyclins from the endothelial cells. These potent vasodilators by decreasing systemic vascular resistance improve the hemodynamics and an increase the exercise capacity. .By blocking its production and by counteracting the adverse effects of AT II ACE inhibition will lead to regression in left ventricular diameters, in other words will cause reverse remodeling and consequently some improvement in systolic function.

Clinical studies supporting the use of ACE-I in patients with HF (Table 1)

The CONSENSUS study is one of the cornerstone studies in HF with regards to the decrease of mortality rates by a drug for the first time (9). In this study, enalapril and placebo were compared in patients with NYHA IV HF symptoms, mostly due to ischemic cardiomyopathy. Digoxin, diuretics, and spironolactone, which were the standard heart failure treatments at the time the study was conducted, were used in both groups. Prior to the completion of patient involvement for the study, it was observed that enalapril provided a 40% relative risk reduction in 6-month mortality and a 31% relative risk reduction in 12-month mortality compared with placebo. Mortality in 1 of 7 patients could be prevented by the use of enalapril. This benefit was maintained up to 4 years and the relative risk reduction was 30% with more than 10 years of follow-up on an average (10).

SOLVD treatment and SOLVD Prevention studies followed the CONSENSUS study, which was the first one (11, 12). In the SOLVD treatment study, enalapril was compared with placebo in patients with mild-to-moderate symptoms, classified as having NYHA II-III, LV ejection fraction (EF) of ≤35%, and HF. It was indicated that enalapril provided a 16% relative risk decrease in mortality and a 26% relative risk decrease in the combined end point, including mortality and hospitalization due to HF. Enalapril prevented mortality in 1 of 22 patients in the SOLVD treatment study.

Enalapril and placebo were compared in the SOLVD Prevention study, which involved asymptomatic patients with LVEF ≤35%. At the end of the three year follow up period although an 8% decrease was seen in mortality using enalapril, it was not significant (p=0.30). On the other hand, enalapril

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decreased the development of symptomatic HF, relatively by 37% and a risk of hospitalization caused by HF by 44%.

In the follow-up analysis of patients in the SOLVD study (both the treatment and prevention studies) for 12 years, significant relative 10% reduction in all cause mortality was detected (p=0.0003). Enalapril increased average life expectancy by 9.4 months (13).

The study in which ACE-I were compared with another effective treatment was V-HeFT II (14). For patients having symptomatic HF (NYHA II-III) and LVEF of ≤45%, there was a 28% decrease in mortality in the 2-year follow-up for the group receiving enalapril treatment compared with that receiving hydralazine-isosorbid dinitrate combination treatment. This study indicated that ACE-I treatment in HF was superior to other vasodilator treatments. In the subgroup analyses, the benefit in survival provided with enalapril were observed only in Caucasian patients; there was no benefit detected in African-American patients.

There are three studies which examined whether ACE-I dose is important in the treatment of HF. The effectiveness of enalapril at different doses (up to 2, 5, 20, and 60 mg) was investigated in two of these studies, and no significant difference was observed (15, 16). As for the ATLAS study, low-dose lisinopril (2.5-5 mg) was compared with high-dose lisinopril (32.5-35 mg). High-dose lisinopril did not decrease mortality; however, there was a 12% decrease in the combined endpoint involving mortality and hospitalization for any reason and a 24% decrease in hospitalization due to HF (17). Althougt it was not randomized, in an analysis evaluated 16,539 patients with a first HF hospitalization, it was observed that mortality decreased in high-dose patients compared with the low-dose patients (18).

In the meta-analysis of five studies [three studies post-myocardial infarction (MI) between 1 and 3 weeks], involving 12,763 patients with reduced LVEF (≤35%; <40%) and/or clinical HF, it was demonstrated that ACE-I provided considerable benefits in the endpoints listed below (19).

- Decrease in all cause mortality. Most of the mortality benefit was due to fewer deaths from progressive HF; this benefit was apparent shortly after the initiation of treatment and gradually increases during the follow-up period (>4 years).
- Decrease in rehospitalization rate due to HF.
- Reduction in MI incidence. No difference in the risk of stroke.

This analysis demonstrates that at least 1 event (death, MI, hospitalization due to HF) is prevented in 7 of every 100 patients treated with ACE-I.

ACE-I in prevention of HF (Table 2)

In three major studies, the effect of ACE-I on various clinical end points (including the development of HF) was investigated in patients having a stable cardiovascular disease with no evidence of HF or LV dysfunction. Among these studies, a 23%

Table 2. ACE-I in prevention of heart failure

	HOPE	EUROPA	PEACE
Number of patients	9297	12.218	8290
Inclusion criteria	>55 years of age, vascular disease or diabetes and other HF risk factor	Stable coronary artery disease	≥50 years of age, stable coronary artery disease
Molecule	Ramipril (10 mg) vs. Placebo	Perindopril (8 mg) vs. Placebo	Trandolapril (4 mg) vs. Placebo
Mean duration of follow-up	5 years	4.2 years	4.8 years
Risk reduction			
HF incidence	23%	39%	
Hospitalization for HF	Not significant		23%

HF - heart failure

decrease in HF incidence was observed with ramipril in the HOPE study (20). The effectiveness of perindopril was evaluated in the EUROPA study, and a 39% decrease in hospitalization due to HF was detected (21). As for the PEACE study, in posthoc analyses, a 23% decrease in hospitalization due to HF was demonstrated with trandolapril (22). A meta-analysis of these three studies did show a significant reduction in the development of HF (2.1%-2.7%, p=0.0007) (23).

ACE-Is in contemporary HF guidelines

In the heart failure guidelines of the European Society of Cardiology (ESC) and American Societies, it is recommended (with class I indication and evidence level A) that an ACE-I should be initiated in all patients with heart failure with reduced EF for decreasing morbidity and mortality, as long as there is no contraindication (1, 2). The results of the clinical studies providing this strong evidence were reported from the last half of the 1980s, and many studies were published one after another. Although ACE-I is strongly recommended in the guidelines for HF treatment, there are also patients who cannot use it due to the side effects. ACE-I may cause deterioration of renal functions, hyperkalemia, symptomatic hypotension, cough, and rarely angioedema. The most common side effect is cough, which can be observed in up to 20% of cases.

Angiotensin receptor blockers in HF treatment (Table 3)

Valsartan

One year after losartan was found to not be more effective than captopril in the ELITE II study conducted with patients having HF and 14 years after CONSENSUS, which was the first ACE-I study, the study "A Randomized Trial of The Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure" (Val-HeFT), conduct-

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Table 3. Large ARB studies conducted in patients with heart failure [adapted from Sayer(8)]

Title of study	ARB	Features of study	Endpoint	Follow-up period (mean/median)	Results
Val-HeFT	Valsartan	n=5010, NYHA II-IV, EF ≤40% (mean 27%), ACE-Iuse 93%,Valsartan (2x160 mg) vs placebo, reaching target dose 84%, mean valsartan dose 254 mg/day	- Mortality associated with all causes - Mortality/HF morbidity	1.9 years	Combined endpoint: - 13% risk reduction with valsartan (RR=0.87; 0.77–0.97; p=0.0009) - 33% risk reduction in patients not receiving ACE-I (p=0.017)
CHARM-Alternative	Candesartan	n=2028, NYHA II-IV EF ≤40% (mean 29.8%), patients not receiving ACE-I, 32 mg/day kandesartan vs. placebo, reaching target dose 59%	Cardiovascular mortality or hospitalization due to HF	33.7 months	23% risk reduction with candesartan (HR=0.77; 0.67-0.89, p=0.0004)
CHARM-Added	Candesartan	n=2548, NYHA II-IV, EF ≤40% (mean 29.8%), ACE-I use 96.32% mg candesartanvs. placebo, reachingtarget dose 61%	Cardiovascular mortality or hospitalization due to HF	41 months	15% risk reduction with candesartan (HR=0.85; 0.75-0.96, p=0.010)
CHARM-preserved	Candesartan	n=3023, NYHA II-IV, EF >40%, ACE-I use 20.32% mg candesartan vs. placebo	Cardiovascular mortality or hospitalization due to HF	36.6 months	No significant risk reduction with candesartan (p=0.118)
ELITE-II	Losartan	n=3152, NYHA II-IV, EF ≤40% losartan 50 mg vs. captopril 50 mg tid	Mortality	1.5 years	17.1% losartan vs. 15.9% captopril (HR=1.13; 0.95-1.35, p=0.16)
HEAAL	Losartan	n=3846, NYHA II-IV, EF ≤40% losartan150 mg vs. losartan 50 mg	Mortality or hospitalization due to HF	4.7 years	10% risk reduction with 150 mg losartan, p=0.027

ARB - angiotensin receptor blocker; ACE-I - angiotensin-converting enzyme inhibitor; EF - ejection fraction; HF - heart failure

ed with valsartan, another angiotensin receptor blocker, was published (24). Despite the ACE-I treatment in HF cases, the observation of high levels of angiotensin II suggested that this molecule may continue its above mentioned adverse effects. The investigators hypothesized that to prevent these detrimental effects by the blockade of angiotensin II might be beneficial and therefore designed the Val-HeFT study, to investigate how the addition of valsartan to ACE-I treatment in patients with HF would affect the clinical outcomes. A total of 5,010 patients with HF, classified as NYHA II-IV and having an average EF of 27%, were randomized either to valsartan or placebo. Two primary end points were defined in the study. The first primary endpoint was all cause deaths. The second primary end point was constituted by combined clinical outcomes, including mortality and morbidity (cardiac arrest necessitating resuscitation, hospitalization due to HF, the use of intravenous inotrope for at least 4 hours, or a vaso-dilator drug). A total of 93% of the patients in both groups, with similar baseline characteristics, used ACE-I. A dose of 40-mg valsartan b.i.d was initiated with the aim to increase the dose to 160 mg bid. During the study, the target dose was achieved in 84% of the cases, and the average dose was 254 mg/day. At the end of the study, a significant difference was not found between the two

groups in the first primary end point (all cause deaths). The death rate in the valsartan group was 19.7%, whereas it was 19.2% in the placebo group. Relative risk (RR) was found to be 1.02 (0.88–1.18; p=0.80). On the other hand, valsartan significantly decreased the incidence of events included by the other primary endpoint (combined endpoint). The incidence of clinical events defined as the combined primary endpoints was 28.8% in the valsartan group, whereas it was 32.1% in the placebo group. These data show that valsartan significantly decreased the event rate (RR 0.87; 0.77-0.97; p=0.0009). These effects were observed homogeneously in all predefined patient subgroups, independent of age, gender, NYHA class, and baseline EF value. When considered with regards to secondary end points defined at the beginning of the study, it was suggested that valsartan was statistically more effective than the placebo in increasing ejection fraction, improving NYHA level, decreasing clinical deterioration, and remitting physical examination findings. Moreover, valsartan decreased hospitalization at the rate of 27.5% (p<0.001), which is among the secondary endpoints and is mostly associated with the quality of life of patients. One subgroup in the Val-HeFT study including 366 cases (185 cases in the valsartan group and 181 cases in the placebo group), who were not able to use ACE-I during the study,

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was evaluated in another study. For the first time, by this sub-group analyses it was demonstrated that an ARB, namely valsartan was superior to placebo in HF (25). While the rate of all cause deaths was 17.3% in the valsartan group, this was 27.1% in the placebo group. This means that valsartan significantly decreased mortality at a rate of 33% (p=0.017). As for the combined primary endpoints, valsartan provided a 44% relative risk reduction compared with the placebo (p<0.001). The EF-increasing effect of valsartan was more striking in the patients not using ACE-I. Besides, a significant regression was detected in the left ventricular inner diameters. Although no significant change was observed in the BNP levels in the placebo group, BNP decreased significantly in patients receiving valsartan. The valsartan dose could be increased to 320 mg/day in 77% of the cases who did not use ACE-I.

The results of the Val-HeFT study, conducted by the addition of valsartan to ACE-I-based treatment in patients with HF, suggested that the hypothesis of the researchers can be true. Both the significant decrease in the combined primary endpoints and increase of physical capacity of the patients taking valsartan in addition to ACE-I treatment, also the recovery of their LVEF and regression of LV diameters, indicate that angiotensin II continues to display its destructive effects in spite of ACE-I treatment. On the other hand, in the cases that could not receive ACE-I, valsartan provided a significant decrease in all clinical outcome end points, including all cause deaths. When compared with CONSENSUS, which was the cornerstone study for RAS suppression in HF, the decrease in mortality rates achieved by enalapril could also be achieved by valsartan.

By considering the 7% of patients who were intolerant to ACE-I therapy, can it be said that ARBs would be used in a small percent of HF patients? This would be an unjust conclusion. Since by design only the patients who were tolerant to ACE-I were recruited to the Val-HeFT study, during the course of the study even this 7% intolerance should be disturbing. In current regitries looking for the rates of ACE-I and ARB use in HF in real life, it can be seen that ARBs are used at a rate of 20%–35% (26-28). In an evaluation made in the Cochrane database, it was detected that the rate of patients quitting the treatment because of undesired effects was 37% lower in the ARB group [RR 0.63 (95% CI 0.52, 0.76)] than in the ACE-I group (29).

Candesartan

Candesartan is another ARB, which had its utility in the treatment of HF investigated by clinical studies. Symptomatic HF patients with several different clinical characteristics were involved in the "Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity" (CHARM) study series in which candesartan was evaluated. These studies are known as CHARM-Added (30), CHARM-Alternative (31), and CHARM-Preserved (32) studies.

In the CHARM-Alternative study, which evaluated the most common clinical scenario, 2,028 patients with symptomatic

(NYHA II-IV) HF, ACE-I intolerance, and LVEF of ≤40% were randomized into placebo or candesartan groups and were followed up for a median period of 33.7 months for the composite primary end point consisting of cardiovascular mortality and hospitalization due to CHF (30). Candesartan was initiated at a dose of 4 or 8 mg/day with a designated target dose of 32 mg/day and this was reached in 59% of the patients. The relative risk reduction for the primary endpoint was found to be 23% (p=0.0004), and number of patients needed to be treated for the prevention of one endpoint was determined to be 14. In the CHARM-Preserved study, 3,023 NHYA II-IV patients with LVEF of >40% were followed up for a median period of 36.6 months (31). The 11% relative risk reduction, in the candesartan group, did not reach statistical significance (p=0.118). In the CHARM-Added study with a median follow-up period of 41 months, candesartan or placebo was administered to patients with LVEF of ≤40%, who almost exclusively were on ACE inhibitor therapy (29). During the study, the rate of reaching the maximum candesartan dose of 32 mg was 61%. At the end of the study, the relative risk reduction for reaching the primary endpoint was 15% in the candesartan group (p=0.010). Unlike other CHARM studies, the discontinuance rate of the drug due to any side effect was found to be higher in the candesartan group compared to the placebo group (p=0.0003).

Losartan and the HEAAL study

After the recognition of the results of the ELITE-II losartan study, which suggested that a 50-mg/day dose of losartan was not as effective as captopril in HFrEF patients, investigation of the efficacy of higher doses of this molecule for this patient group became an issue (2). In the HEALL study designed within this context, 3,846 patients with LVEF of ≤40%, NYHA II-IV, and intolerance to ACE-I were randomized to low-dose (50 mg) or high-dose (150 mg) losartan, and they were followed up for a median period of 4.7 years for the primary endpoint of hospitalization due to CHF (33). At the end of the study, the primary endpoint was reached 46% in the low-dose losartan group and 43% in the high-dose losartan group (p=0.027), indicating the importance of optimal dosing during ARB administration (2).

ARBs in contemporary HF guidelines

The Heart Failure Guidelines of the American College of Cardiology and American Heart Association published in 2013 mentioned valsartan, candesartan, and losartan and recommended these drugs to be initiated at doses of 20-40 mg bid, 4-8 mg od, and 25-50 mg od, respectively, and target doses of 160 mg bid, 32 mg od, and 150 mg od respectively, in symptomatic or previously symptomatic HFrEF patients. The use of ARBs for decreasing morbidity and mortality in HFrEF patients who cannot tolerate an ACE-I is a class 1 recommendation (level of evidence A). In HFrEF patients, the use of ARBs as the first line drug alternative to ACE-I is given a class IIa indication (level of evidence A), and this is emphasized especially for patients receiving ARBs for other

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reasons. On the other hand, in HFrEF patients using an ACE-I and beta-blocker, the addition of ARBs is considered a class IIb recommendation if patients cannot tolerate an aldosterone antagonist or if an aldosterone antagonist is contraindicated (level of evidence A). However, the routine combination of an ACE-I, an aldosterone antagonist, and an ARB is reported to be harmful, with a class III recommendation and level of evidence C. In the American guidelines, hypertensive cases (stage A) with a high risk of developing HF are recommended to use ARB. ARBs are emphasized with a class IIa indication (level of evidence C) as well as ACE-I and beta-blockers. Furthermore, it is specified that ARBs can be given with a class IIb indication (level of evidence B) to decrease hospitalization due to CHF, in addition to their use as antihypertensive medication (2).

In the Acute and Chronic Heart Failure Diagnosis and Treatment Guidelines published by the ESC in 2012, ARBs are recommended as class 1, evidence level A for HFrEF patients not receiving ACE-I. Furthermore, ARBs are included in this guideline as class 1, evidence level A, for decreasing hospitalization due to HF in patients with a LVEF of ≤40% who do not use an aldosterone antagonist and who has NYHA II-IV symptoms while on ACE-I and beta-blockers (1).

Conflict of Interest: Prof. Zeki Öngen is a member of Novartis' Advisory Board.

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