Valsartan after myocardial infarction

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Abstract

One of the important problems of the patients undergoing acute myocardial infarction (MI) is early development of heart failure. It has been revealed in various studies that renin-angiotensin-aldosterone system (RAAS) has a significant role in this process. The studies conducted with angiotensin converting enzyme (ACE) inhibitors have resulted in decreased mortality rate. Another RAAS blocker which was discovered about ten years later than other ACE inhibitors in historical process is angiotensin receptor blockers (ARB) inhibiting the efficiency of angiotensin 2 by binding to angiotensin 1 receptor. Valsartan is one of the molecules of this group, which has higher number of large-scale randomized clinical studies. In this review, following presentation of a general overview on heart failure after acute MI, the efficiency of ARBs in this patient group will be discussed. This discussion will mostly emphasize the construction, outcomes and clinical importance of VALIANT *(VALsartan In Acute myocardial iNfarcTion)*, which is the study on valsartan after acute MI heart failure. *(Anadolu Kardiyol Derg 2014; 14(Suppl 2): S9-S13)*
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Myocardial infarction (MI) is a fatal disease. Its effects are catastrophic to the health of the patient, even if it does not result in death. When discharged from the hospital, patients are mostly unaware of the years of life lost. Many patients think that they have survived a heart attack and recovered. Moreover, patients are unaware that they will experience a condition called heart failure in the near-middle future, the progression of which varies according to the amount of heart muscle loss, and that they will miss to breathe without difficulty. Fortunately, we, the physicians, know very well that a patient who has had a heart attack will never be as healthy as he/she was previously, and that lost cardiac muscle will never be regenerated, the injury may extend to surrounding healthy tissues if appropriate treatment is not provided, and this may lead to the deterioration of the patient's overall condition. This is why we, physicians primarily strive to implement preventive measures against heart attacks in our patients. We struggle with hypertension, smoking, and cholesterol and tirelessly explain the importance of primary protection. However despite these efforts, we cannot reduce the incidence of this disease to zero and prevent the overflow of coronary care units; nevertheless, we never lose heart or accept that we are unable to prevent MIs. We primarily strive to ensure the survival of patients presenting with acute MI, and if possible, provide recovery without or at least with minimal damage. For this purpose, we utilize all the opportunities offered by modern medicine. Hence, in the light of available evidence, this article evaluates the role of valsartan, an angiotensin receptor blocker (ARB), in the treatment of patients developing heart failure in the early stages after acute MI.

Acute myocardial infarction and the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a prerequisite for the survival of human beings. Despite this fact, when it comes to RAAS, we, cardiologists always think about the chain of events working against the heart. The reason for that is the fact that RAAS plays an active role in the physiopathology of many diseases in our field of interest. Angiotensin II, a product of RAAS, has a series of toxic effects on the cardiovascular system, such as vasoconstriction, activation of the sympathetic nervous system and vasopressin, increasing endothelin release, and facilitating platelet aggregation. Furthermore, angiotensin II also has some properties that negatively affect the occurrence and development of heart disease, including facilitation of thrombosis by increasing levels of tissue plasminogen activator, mediation of ventricular remodeling through myocardial hyper-

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trophy and collagen accumulation, and increasing aldosterone synthesis (1, 2). Regarding MI, there are many studies that support the fact that angiotensin II plays a role in all processes, from the formation and development, to weakening and rupture of atheromatous plaques, and finally to the thrombotic occlusion of the coronary artery (3). Based on an understanding of the importance of RAAS in the course of coronary artery disease, studies investigating the potential benefits of the RAAS blockade have been conducted. Large-scale randomized clinical trials such as the Heart Outcomes Prevention Evaluation (HOPE) (4) and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) (5) assessed the effects of therapy with angiotensin-converting enzyme (ACE) inhibitors in patients with stable coronary artery disease and demonstrated that the risk of MI could be reduced, and that the prognosis could be improved with this medication. The positive effect of ACE inhibitors on the prognosis of patients with heart failure (6, 7) has led to a belief that they can also be effective in treating early left ventricular dysfunction after MI. This belief is further strengthened by understanding the active role of RAAS in the remodeling of the left ventricle (8), which has an important role in the development of heart failure after MI. Studies investigating the effects of captopril [Survival and Ventricular Enlargement (SAVE)], ramipril [Acute Infarction Ramipril Efficacy (AIRE)], and trandolapril [Trandolapril Cardiac Evaluation (TRACE)] in patients developing heart failure after acute MI, revealed a significant decrease in the number of cardiovascular events, including total mortality (9-11). Eventually, ACE inhibitors were included in the recent treatment guidelines with a class 1 indication in this patient group.

ARBs Following Acute MI

Despite the success achieved with ACE inhibitors, researchers observed that administration of the maximum dose of ACE inhibitors failed to completely prevent angiotensin II generation (12). Researchers also noticed development of a cough as a side effect in a considerable amount of patients. These two observations led to new research that investigated the pharmacologic strategies for RAAS blockade (13). Consequently, in the mid-1990s, the first ARB molecule, losartan, was introduced to the medical community (14).

As is known, ARBs, whether generated by ACE or non-ACE pathways, act by blocking the angiotensin 1 receptor, which mediates the adverse effects of angiotensin II. Thus, they also block the effects of angiotensin II that escapes from the ACE inhibitor blockade. Moreover, unlike ACE inhibitors, ARBs do not prevent bradykinin degradation. Although these characteristics were initially considered to be superior to ACE inhibitors by some experts, others demonstrated the positive effects of bradykinin on the cardiovascular system (15), suggesting that ARBs may not achieve the same level of success as that achieved by ACE inhibitors.

The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial, which was the first study to assess the effects of losartan, created a highly important perception that ARBs provide a benefit beyond reducing blood pressure by surpassing atenolol in hypertensive patients with left ventricular hypertrophy (16). Consequently, large clinical studies were designed to test this new molecule for the treatment of various diseases. Among these studies, is a randomized clinical trial known as Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL). In this study, half of the 5,500 patients who developed heart failure after acute MI were randomized to receive 50 mg captopril three times daily, which was previously proven to be effective; the other half was randomized to receive 50 mg losartan daily (17). The rate of all-cause mortality, which was the primary endpoint, was found to be similar between the two groups after an average follow-up period of 2.7 years (losartan: 18%, captopril: 16%, p=0.07). However, because the p-value supported a trend in favor of captopril, while the hypothesis of the study was based on the superiority of losartan, this study could not establish the non-inferiority of losartan, an ARB to ACE inhibitor. Although the failure of losartan was explained by the maintenance of systolic blood pressure approximately 5 mm Hg lower in the captopril group during the study, and by the preference of administering losartan at a relatively low dose of 50 mg, the OPTIMAAL study was considered as a negative ARB study that could not prove its primary hypothesis concerning the efficacy of ARB.

After the identification of losartan, many other molecules were added to the family of ARBs. Among the family of ARBs, much attention has been paid to valsartan, an ARB molecule with the greatest number of studies published in the cardiovascular field.

Valsartan after acute MI: The Valsartan in Acute Myocardial infarction (VALIANT) Study (18)

Valsartan has been studied in many randomized clinical trials, since the first day of its discovery. Some of these studies include Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) in the field of hypertension (19), MicroAlbuminuria Reduction with Valsartan (MARVAL) in the field of proteinuria (20), and Valsartan Heart Failure Trial (Val-HeFT) in the field of heart failure (21). Following the clinical success achieved in these studies, valsartan was considered for the use of left ventricular failure after MI, in which other ARBs have performed poorly. Although the Val-HeFT study provided positive results and indicated that valsartan could be successful in the treatment of patients with early heart failure after MI, negative results obtained in the OPTIMAAL study with losartan has led to concerns of a new failure. Consequently, the VALIANT study was conducted taking such concern into consideration. In this study, which included 931 centers from 24 countries, the administration of 160 mg valsartan b.i.d was compared to the administration of 50 mg captopril t.i.d. Moreover, in addition to the ARB versus ACE inhibitor concept, ARB + ACE inhibitor combination versus monotherapy with either ARB or ACE inhibitor was also

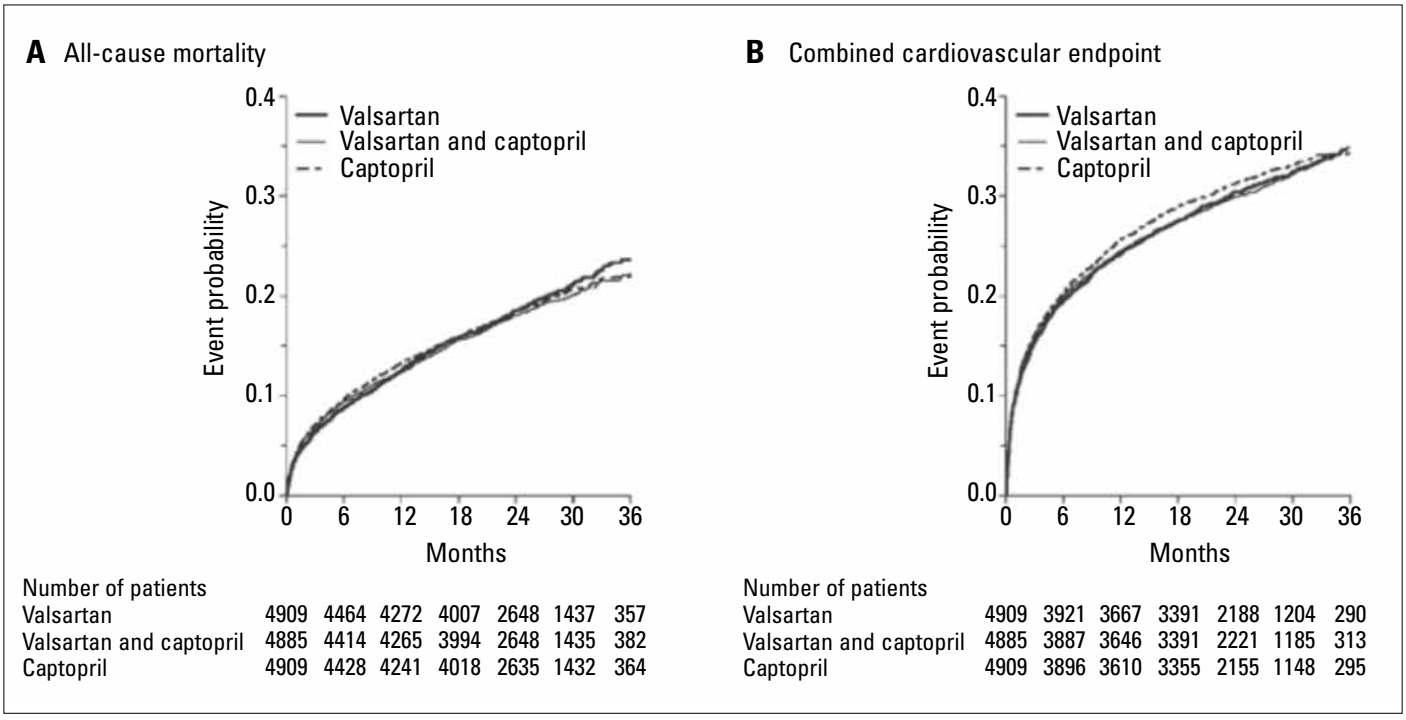

Figure 1. Kaplan-Meier statistical analysis of all-cause mortality rate (Panel A), the rate of cardiovascular death and hospitalization rates due to reinfarction or heart failure (Panel B) according to treatment groups is shown. For all-cause mortality rate, the comparison of valsartan with captopril, p=0.98; comparison of the valsartan + captopril group with the captopril group, p=0.73; for death due to cardiovascular reasons and reinfarction or heart failure, comparison of the valsartan group with the captopril group, p=0.20 and comparison of the valsartan + captopril group with the captopril group, p=0.37

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tested in the VALIANT study. The main hypothesis of VALIANT was that valsartan was non-inferior to captopril. The primary endpoint of the study was all-cause mortality, and the secondary endpoint was the combination of cardiovascular death and hospitalization due to nonfatal MI and heart failure. All 14,703 patients included in the study had clinically or radiologically confirmed heart failure in the early period after acute MI. There was no statistically significant difference between the valsartan and captopril groups in terms of variables that could have an effect on study outcomes such as age, gender, medications, comorbid diseases, and degree of heart failure. During the mean follow-up period of over 2 years (median follow-up, 24.7 months), the blood pressure values were similar in the valsartan and captopril groups.

When the data were analyzed with regard to the primary endpoint, it was found that captopril and valsartan showed the same success in the prevention of all-cause mortality (19.5% versus 19.9%; p=0.98) (Fig. 1). Since the efficacy of ACE inhibitors for heart failure after MI had been previously demonstrated, it was not possible to compare valsartan with a placebo in the VALIANT study. This was due to the ethical necessity of comparing a novel treatment strategy (ARB) with the best treatment available (ACE inhibitors). Nevertheless, to explore the comparison of valsartan to a placebo, the researchers developed a statistical model that compared the SAVE, TRACE, and AIRE studies, which had been previously conducted to compare an ACE inhibitor with a placebo, to the VALIANT study. This analysis included in the original VALIANT article, concluded that mortality would have been decreased at a rate of 25% if valsartan had been compared to a placebo. This is a highly significant decrease in mortality. On the other hand, as seen in Figure 1, no significant difference was detected between the two groups in terms of secondary endpoint variables. In an analysis that examined only the coronary endpoints of the VALIANT study, which was published later, the rates of fatal and nonfatal MI were found to be similar between the two treatment groups (22). Another research question concerned a combination group, which consisted of individuals who received a combination of an ACE inhibitor and an ARB. Individuals who expected the superiority of the combination of an ACE inhibitor with an ARB to monotherapy of either of the two agents, unfortunately, were disappointed. The use of the two drugs together did not yield better results compared to the use of a single drug; additionally more side effects were reported in the combination group (18).

Clinical significance of the VALIANT study

The VALIANT study was the first and only study showing that valsartan is not inferior to ACE inhibitors in decreasing all-cause mortality in the presence of heart failure after MI. When the size

of the patient population and statistical value of the results were evaluated together, it was evident that there was no possibility that this finding was incidental. Therefore, it can be said that the VALIANT study established a new treatment alternative for heart failure after acute MI.

Following this study, as in other large clinical studies, a discussion was started about whether this positive effect should be attributed to only valsartan or whether all ARBs should share this indication. It was concluded that the positive effect obtained in the VALIANT study could not be evaluated as a group effect. The first basis of this is the losartan example. Unlike the success achieved with valsartan in the VALIANT study, the OPTIMAAL study could not achieve successful results with losartan in comparison to 150 mg/day captopril. The second basis is the uncertainty in dosage. As is known, the presence of a group effect is accepted in ARBs when hypertension treatment is in question. This is because we know the extent of decrease in blood pressure that is provided by a particular dose of a particular ARB. However, in specific situations, such as in the period after MI, the effective and reliable doses of ARBs, except valsartan, are unknown. For instance, when we decide to initiate candesartan in a patient after MI, considering a group effect, it is unclear which dose should be chosen (8, 16, 32, 64 or 128 mg). This uncertainty is also valid for other ARBs. If the VALIANT study had not been performed, and if we had planned to initiate valsartan in a patient after MI, we would most probably prefer 160 mg valsartan once daily, which is similar to the dose of valsartan administered when the drug is used as an antihypertensive, instead of 160 mg two times daily. Presumably, we would not achieve the expected benefit in the end, as the required dose was not used. Therefore, it seems that the most rational method is to choose the proven ARB at its proven dosage. Considering these reasons, only valsartan has been mentioned in the recent acute MI treatment guidelines of the European Society of Cardiology when referring to ARBs as alternatives to ACE inhibitors in case of early heart failure (23). Owing to the VALIANT study, valsartan, with a strong class 1B indication, has been included in the guidelines as an important part of treatment for this patient group.

Conflict of Interest: Prof. Sadi Güleç is a member of Novartis' Advisory Board.

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