

# DUAL RENIN ANGIOTENSIN SYSTEM BLOCKADE IN HEART FAILURE AND IN MYOCARDIAL INFARCTION

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## REZUMAT

Antagonizarea sistemului renină-angiotensină a devenit în ultimii ani o abordare terapeutică de succes, având ca rezultat scăderea mortalității globale și cardiovasculare, atât în cazul pacienților cu insuficiență cardiacă, cât și în cazul celor cu infarct miocardic. Numeroase studii clinice au stabilit valoarea terapiei cu inhibitori ai enzimei de conversie a angiotensinei la acești pacienți. Studiile clinice mai recente compară terapia combinată (inhibitori ai enzimei de conversie a angiotensinei cu antagoniști ai receptorilor AT 1 ai angiotensinei II) cu monoterapiile respective la pacienții cu infarct miocardic și la cei cu insuficiență cardiacă. În contrast cu cele mai recente două studii care au inclus pacienți cu insuficiență cardiacă (CHARM-Added și Val-HeFT), în care terapia combinată și-a dovedit eficiența în scăderea mortalității și morbidității cardiovasculare, trialul VALIANT nu a reușit să demonstreze superioritatea terapiei combinate la pacienții cu infarct miocardic acut complicat cu insuficiență cardiacă la debut. Câteva studii experimentale și clinice au asociat terapia cu antagoniști ai receptorilor AT 1 ai angiotensinei II cu un risc crescut de apariție a infarctului miocardic, dar mai multe meta-analize riguroase au infirmat această ipoteză. Dubla antagonizare a sistemului renină-angiotensină și-a dovedit efectul benefic în ameliorarea funcției ventriculare stângi, fără a crește mortalitatea globală, mortalitatea și morbiditatea cardiovasculară.

**Cuvinte cheie:** inhibitorii enzimei de conversie a angiotensinei, antagoniștii receptorilor AT 1 ai angiotensinei II, insuficiență cardiacă, infarct miocardic, remodelare ventriculară

## ABSTRACT

Blockade of the renin-angiotensin system has become one of the most successful therapeutic approaches in recent years, leading to a decrease in cardiovascular morbidity and mortality in patients with chronic heart failure as well as in patients with myocardial infarction. Multiple well-known randomized clinical trials have established the value of the angiotensin-converting enzyme inhibitors in these patients. Several more recent trials have compared combination therapy with angiotensin receptor blockers and angiotensin-converting enzyme inhibitors with the respective monotherapies in patients with MI and in patients with chronic heart failure. In contrast to the most recent trials involving patients with chronic heart failure (CHARM-Added and Val-HeFT) in which dual renin-angiotensin system blockade was shown to be beneficial in terms of cardiovascular morbidity and mortality, VALIANT trial failed to demonstrate the superiority of combination therapy in improving survival in patients with acute myocardial infarction complicated with heart failure. Some experimental and clinical studies associate angiotensin II AT1 receptor blockers therapy with an unexplained increase in myocardial infarction, but several rigorous meta-analyses did not confirm this hypothesis. The dual renin-angiotensin system blockade has proved its beneficial effect on the improvement of the left ventricular function, without increasing all-cause mortality, cardiovascular mortality and morbidity.

**Key Words:** angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heart failure, myocardial infarction, left ventricular remodeling

## INTRODUCTION

Heart failure is the leading cause of death and hospitalization in the developed world. Pharmacotherapy for heart failure has advanced considerably in recent years. Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II

AT 1 receptor blockers (ARBs) has become one of the most successful therapeutic approaches in medicine. RAS blockade results in a decrease in cardiovascular morbidity and mortality in patients with chronic heart failure (CHF) as well as in patients with myocardial infarction (MI).

It is well known that activation of the RAS is the major determinant of left ventricular (LV) remodeling, playing a crucial role in the pathogenesis of heart failure. LV remodeling is the process by which ventricular size, shape and function are regulated by mechanical, neurohormonal and genetic factors.<sup>1</sup> LV remodeling may be physiological and adaptive during normal growth and pathological in MI, cardiomyopathy, hypertension or valvular heart disease when leads to LV dysfunction with progressive deterioration to increasing grades of heart failure.

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LV remodeling after MI is a complex, dynamic and time-depending process and progresses in parallel with healing over months.<sup>1,2</sup> The acute loss of myocardium is an abrupt increase in loading conditions that induces a unique pattern of remodeling involving both the infarcted and noninfarcted zone, which is different from remodeling in stable CHF.<sup>1</sup>

CHF and MI are two different disease states. After MI, the rate of clinical events is much higher in the first 6 months whereas in stable CHF there is a more linear rate of adverse outcomes. Patients with MI are more likely to have further acute coronary events whereas patients with CHF are more likely to experience worsening heart failure leading to hospitalization.<sup>3</sup> The intersection of acute heart failure in the setting of AMI defines a high-risk group that experiences a disproportionate number of fatal and non-fatal cardiovascular events.<sup>4</sup> These clinical and pathological differences between the heart failure in MI and stable CHF could be reflected in a different response to various drug therapies.

## **CLINICAL TRIALS WITH DUAL RAS BLOCKADE**

It is well known that multiple randomized clinical trials have established the value of the ACE inhibitors in reducing mortality rates and major nonfatal cardiovascular events in patients with CHF caused by systolic dysfunction and in those with MI.<sup>5</sup>

Several more recent trials have compared combination therapy with ARBs and ACE inhibitors (dual RAS blockade) with the respective monotherapies in patients with MI complicated with heart failure and in patient with CHF.

The RESOLVD study evaluated 768 patients with NYHA Class II-IV heart failure who were randomized to receive candesartan, enalapril, or their combination; patients were evaluated over a period of 43 weeks. There was found a no significant increase in LVEF in the combination group. Significant differences were found in favor of the combination therapy in regard to ventricular volumes. Death and hospitalizations for heart failure did not differ among the three groups.<sup>6</sup> However, this appears to be the first relatively large-scale study documenting that dual RAS blockade appeared to significantly attenuate ventricular remodeling when compared with either agent alone.<sup>7</sup>

McKelvie et al carried out a comparative study using the RESOLVD study population. They compared the impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodeling in patients with congestive heart failure. They demonstrated that

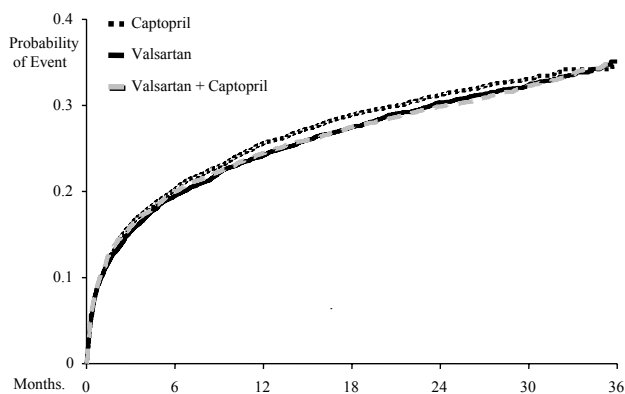
the triple therapy has a more beneficial effect on LV volumes and LVEF than the respective monotherapies or dual therapies.<sup>7</sup>

Val-HeFT trial randomized 5010 patients with heart failure of NYHA class II-IV to placebo or valsartan titrated to 160 mg twice daily, in addition to their background therapies (including ACE inhibitors in 93% and beta-blockers in 35% of the patients).<sup>8</sup>

Mortality was similar in the two treatment groups. The combined end-point mortality and morbidity was significantly lower (13.2% reduction in risk) with valsartan than with placebo. The major effect of valsartan was a 27.5% reduction in the incidence of hospitalizations for heart failure, demonstrating that the drug was effective in slowing the progression of disease.<sup>9</sup>

The benefit of valsartan on outcome was associated with a highly significant increase in LVEF and reduction in LV diastolic diameter than in the placebo group.<sup>10</sup>

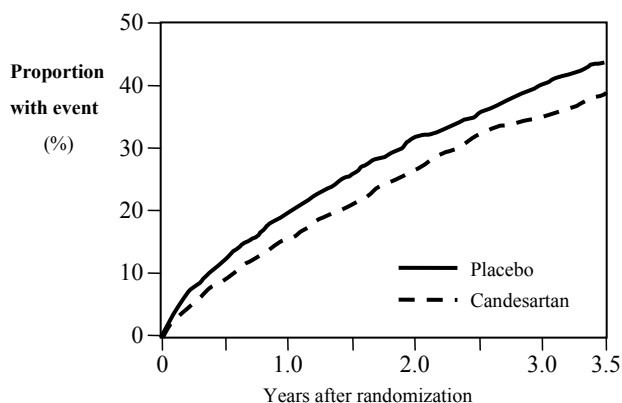
VALIANT, a double-blind randomized trial, the largest study of an ARB to date, compared the effect of the ARB valsartan, the ACE inhibitor captopril, and the combination of the two on mortality in patients with acute MI complicated with heart failure. Patients were randomly assigned, 0.5 to 10 days after acute MI. The primary end-point was all-cause mortality. The trial concluded that valsartan is as effective as captopril in patients who are at high-risk for cardiovascular events after MI and that combined therapy increased the rate of adverse events without improving survival.<sup>11</sup> VALIANT echo substudy, consisting of 610 patients, representing a modern post-MI cohort in whom all received effective inhibition of the RAS and having serial echo data (at 3 and 20 months), revealed that treatment with captopril, valsartan, and the combination of valsartan and captopril was associated with similar changes in ventricular size and function.<sup>12</sup> (Fig. 1)



**Figure 1.** VALIANT Study: Combined end-point (cardiovascular death, myocardial infarction and heart failure). Valsartan vs. Captopril: HR = 0.96; P = 0.198; Valsartan + Captopril vs. Captopril: HR = 0.97; P = 0.369. (Adapted with permission from Pfeffer et al)<sup>11</sup>

In contrast with VALIANT, OPTIMAAL trial showed that captopril was associated with no significant lower all-cause mortality and a significant lower cardiovascular mortality compared to Losartan.<sup>13,14</sup>

CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program (7601 pts.) consisted of 3 independent but linked trials, two of which randomized patients with LV systolic dysfunction and the third included patients with heart failure and preserved LV systolic function. In CHARM-Added 2548 patients taking an ACE inhibitor (in more than half of the patients, a beta-blocker also) were randomized to either placebo or a target dose of candesartan 32 mg once daily. The risk of the primary outcomes in this trial, death from a cardiovascular cause or hospitalization for worsening CHF, was reduced significantly by 15% with candesartan. Candesartan led to a prominent reduction in hospitalizations for worsening CHF.<sup>3</sup> (Fig. 2)



**Figure 2.** Cardiovascular death or hospital admission for CHF in CHARM-Added trial. Hazard ratio 0.85 (95% CI 0.75-0.96);  $P = 0.011$ . (Adapted with permission from Granger et al)<sup>15</sup>

In CHARM-Alternative 2028 patients with prior intolerance of an ACE inhibitor were randomized to either placebo or candesartan. The risk of death from a cardiovascular cause or hospitalization for worsening CHF was reduced significantly by 23% with candesartan.<sup>3,15</sup>

In CHARM-Preserved 3023 patients with CHF and preserved LV systolic function (LVEF > 40%) were randomized to candesartan (titrated to 32 mg daily) or placebo. Candesartan did not lead to a statistically significant reduction in cardiovascular death, although there was a substantial and significant reduction (16%) in heart failure hospitalization.<sup>3</sup>

## **ARB'S AND CARDIOVASCULAR PROTECTION**

In the past year there has been fervent debate whether ACE inhibitors and ARBs offer similar

coronary vascular protection.

In a recent review, Verma and Strauss studied a meta-regression analysis of 21 large-scale trials presented by BPLTTC (The Blood Pressure Lowering Treatment Trialists' Collaboration) and have shown a highly statistically significant benefit of ACE inhibitors relative to ARBs on MI and cardiovascular death.<sup>16</sup> Furthermore, some isolated trials associate ARBs therapy with an unexplained increase in MI. For example, VALUE trial was designed to test the hypothesis that, for the same level of blood pressure (BP) control, valsartan-based therapy would be superior to amlodipine-based therapy in reducing cardiovascular morbidity and mortality. Although Verma and Strauss recognize the central importance of BP reduction towards vascular protection, in their opinion a 1.8/1.5 mmHg blood pressure differential in favor of amlodipine over valsartan in VALUE trial could not explain the 19% excess of MI events in the valsartan group. However, the VALUE investigators entirely attributed the higher incidence of MI in the valsartan group to the lesser antihypertensive effect in that group.

Verdecchia et al carried out another meta-analysis of 11 trials that included 31958 patients randomized to ARBs and 32423 patients randomized to either placebo or different drug classes. The authors concluded that treatment based on ARBs was associated with a non-significant 4% lesser risk of MI compared with placebo and a non-significant 1% lesser risk of MI compared with ACE inhibitors. Treatment based on ARBs was associated with a slightly higher risk of MI when compared with drug classes different from ACE inhibitors. Similar to MI, all-cause mortality and cardiovascular mortality did not differ between ARBs and drugs different from ARBs.<sup>17</sup>

McMurray claims that the analysis of Verma and Strauss is incomplete and inaccurate because of the heterogeneity of the considered trials and because they did not cite the two largest studies (OPTIMAAL and VALIANT) that randomized patients to an ACE inhibitor or ARB and had the statistical power to evaluate cardiovascular outcomes. These two studies had twice as many MIs as their trials combined. In McMurray's opinion, as none of their trials randomized these two treatments, their conclusions depend on indirect comparisons, small numbers of events and are unreliable.<sup>18</sup>

Another meta-analysis of about 32,000 patients, performed by McDonald et al concluded that using ARBs was not associated with a significant increase in the risk of MI as compared to ACE inhibitors or

placebo. Subsequently ARBs are considered a safe and effective alternative for patients with heart failure and intolerance to ACE inhibitors.<sup>19</sup>

The issue of the cardiovascular protection of ARBs will be clarified in the future by the results of two ongoing trials – ONTARGET and TRANSCEND – that randomized patients at high-risk of developing cardiovascular disease.<sup>20</sup>

### **TRIPLE THERAPY WITH ACE INHIBITORS, ARB'S, BETA BLOCKERS AND MORTALITY**

ACE inhibitors and beta-blockers reduce mortality and morbidity in heart failure patients. They also beneficially affect LV dilatation. ARBs have been compared to ACE inhibitors in heart failure patients. No clear differences in mortality, morbidity or impact on LV dilatation have been demonstrated.<sup>7</sup>

In the Val-HeFT trial, patients already treated with ACE inhibitors did not have any mortality benefit of adding an ARB and in patients already treated with both ACE inhibitors and beta-blockers all-cause mortality was increased. A subgroup analysis was necessary to explore possible differences in response in patients taking previously ACE inhibitors, beta-blockers, both or neither. This analysis was most revealing. The efficacy of valsartan in patients not taking an ACE inhibitor before randomization was highly significant on both mortality (33% reduction) and morbidity (44% reduction). This subgroup represented only 7% of the Val-HeFT population and this favorable effect did not have much impact on the overall results of the trial. The benefit was of modest significance in patients taking an ACE inhibitor. Furthermore, patients on low-dose ACE inhibitor had a greater benefit of adding valsartan than those on high dose.<sup>10</sup>

In the subgroup of patients receiving both an ACE inhibitor and beta-blocker as background therapy the addition of valsartan was associated with a higher mortality and a trend for a higher morbidity. This adverse effect of the triple therapy might have been a statistical anomaly, because the ventricular remodeling or the neurohormonal data did not reveal an adverse trend and blood pressure did not fall any more than in the other subgroups.<sup>8</sup>

McKelvie et al designed a study based upon a cohort of 426 patients from RESOLVD population who were considered eligible to receive beta-blocker treatment. According to the original RESOLVD protocol, all patients were initially randomized to receive either candesartan, enalapril or their combination. After 19

weeks of treatment, patients were randomized to either metoprolol therapy or placebo in addition to original treatment, and then followed-up for 43 weeks. Patients were divided into four groups according to treatment: (1) ARB or ACE inhibitor as monotherapy, (2) ARB and ACE inhibitor as double therapy, (3) beta-blocker in double therapy with either ARB or ACE inhibitor or (4) beta-blocker in triple therapy with ARB and ACE inhibitor. LVEF, LV volumes, and neurohormonal analyses were measured at randomization and after 43 weeks.

The primary result was a significant improvement in LVEF when triple therapy was compared with any of the other treatment regimens. There was a no significant improvement in LVEF when candesartan was added to captopril and when metoprolol was added to either treatment.<sup>21</sup>

This study has demonstrated that triple therapy is well tolerated in patients with heart failure and has the potential for providing further benefit in these patients. Data from other studies demonstrated that survival is better in patients with smaller cardiac volumes but the size of the study was too small to evaluate whether the changes in cardiac volumes translate into an improvement in clinical events.<sup>7</sup>

In the CHARM-Added trial, the efficacy of candesartan was not altered by baseline use of a beta-blocker in addition to an ACE inhibitor. Patients receiving triple therapy had similar incremental reductions in cardiovascular mortality and heart failure hospitalizations.<sup>3</sup>

VALIANT trial, in which approximately 70% of the patients were taking a beta-blocker at the time of randomization, showed no adverse interaction with valsartan and no increased risk associated with triple therapy in patients with MI complicated by heart failure, LV dysfunction, or both.<sup>11</sup>

VALIANT and CHARM-Added trials have clearly demonstrated that triple therapy doesn't increase all-cause mortality or cardiovascular mortality.

### **SAFETY AND TOLERABILITY OF DUAL RAS BLOCKADE**

The price to be paid for combining an ACE inhibitor with ARB will be the addition of side effects, those dependent on ACE inhibition (cough, angioneurotic edema), the increased risk of functional renal insufficiency, hypotension and hyperkalemia. There is undoubtedly an increased risk for some patients exposed to an intensified blockade of the RAS by high doses of a single-site blocker or combined

usual doses of two RAS blockers: elderly or salt-depleted patients, patients receiving cyclooxygenase inhibitors, patients with renal artery stenosis, and during anesthetic induction.

In the CHARM-Added trial, 4.5% of the candesartan-treated patients with CHF compared with 3.1% of the placebo-treated patients experienced significant hypotension that led to treatment interruption. In addition, the incidence of significant creatinine increase was almost doubled in the candesartan group (7.8% versus 4.1% in the placebo group), as was the incidence of hyperkalemia, especially when spironolactone was part of the therapy. In the VALIANT trial, dual RAS blockade increased the rate of intolerance to treatment and permanent discontinuation of study treatment.<sup>22</sup>

The usual once-daily doses of ACE inhibitors and ARBs were selected initially on the basis of hypertension trial results, but the dose response for preventing cardiovascular death in patients with CHF may not be the same as for BP reduction. All the results from randomized controlled clinical trials have demonstrated that the higher the doses of the ACE inhibitor and the ARB, the greater the effect on target-organ damage. The combination of two RAS blockers maximizes the cardioprotection afforded by even high doses of single-site RAS blockers. It maintains over 24 hours a permanent and complete blockade of the RAS, which is more easily achieved by combining two different RAS blockers than by increasing the once-daily dose of a single drug. By making possible a once-daily administration to achieve permanent blockade of the RAS over 24 hours, dual RAS blockade may also improve treatment compliance.

A more complete and rigorous assessment of these risks requires pharmacoepidemiological studies of a large number of diverse patients with hypertension, renal insufficiency and CHF in the general population.

## **BASIC RESEARCH**

The RAS plays a key role in structural and functional remodeling after MI, and angiotensin (Ag) II is a major determinant of this process. Ag II stimulates cardiac hypertrophy and fibrosis in ischemic heart failure models, whereas Ag II blockade prevents development of LV remodeling and hypertrophy after MI.<sup>23</sup> Remodeling is associated with elongation of noninfarcted myocardial segments and cellular hypertrophy. Cardiovascular effects of Ag II include vasoconstriction, cellular hypertrophy, and interstitial fibrosis.<sup>24</sup>

In a rat postinfarction model, for example, it has been shown that AT1 receptor blockade decreases peripheral vasoconstriction, attenuates LV remodeling, and it is equivalent to ACE inhibition in improving survival. After MI, there was a 67% increase in myofibrillar collagen. The attenuation of LV remodeling after MI by AT1 receptor blockade is accompanied by specific effects on myocardial contractile function and prevention of abnormal passive myocardial stiffness.<sup>25</sup>

Myocardial protection by preconditioning of heart with losartan in rats showed significant postischemic ventricular recovery, demonstrated by improved developed pressure of aortic flow and reduced MI size. Losartan provided cardioprotection in two ways: (1) by reducing infarct size and improving ventricular function and (2) by inhibiting cardiomyocyte apoptosis. Although ACE antagonism or AT1 receptor blockade has been found to mimic preconditioning, the mechanism of action remains unclear. It has been reported that ACE inhibitors function in part by preserving bradykinin. The cardioprotective effects of losartan against ischemia in rat hearts seem to be also bradykinin-dependent.<sup>26</sup>

Another study in rats showed that ACE inhibitors and ARBs reversed ventricular remodeling by a mechanism independent of changes in BP.<sup>23</sup>

The combination of ACE inhibitor and ARB, independently of the hypotensive effect, improved LV phenotypic change and increased LV endothelin-1 production and collagen accumulation, improved LV dysfunction and survival in a rat heart failure model more effectively than either agent alone, thereby providing strong experimental evidence that the dual RAS blockade is more beneficial than monotherapy for treatment of heart failure.<sup>27-29</sup>

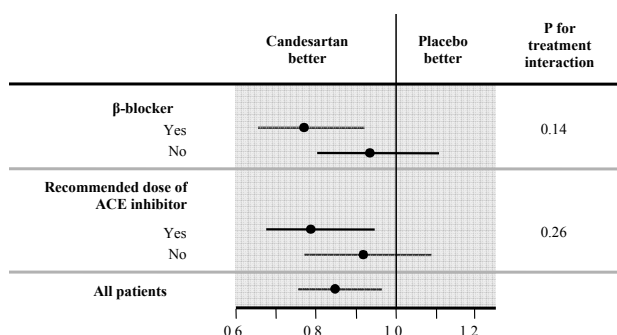
## **DISCUSSIONS**

In contrast to the two trials involving patients with CHF (CHARM-Added and Val-HeFT) in which dual RAS blockade was shown to be beneficial in terms of cardiovascular morbidity and mortality, the combination arm of VALIANT showed an increased rate of adverse events without improving survival.<sup>30</sup>

The differences in study samples (patients who had recently had MI versus those with CHF of various causes), the drug titration (add-on therapy versus concurrent up-titration), and the dosages used may explain this discrepancy.<sup>14</sup> In the mentioned heart failure trials, ARB therapy was added to preexisting ACE inhibitor therapy, so the two treatments were

not started at the same time, neither were the doses titrated concurrently.

In VALIANT patients received a proven dose of a proven ACE inhibitor to which valsartan was added. In contrast, the ACE inhibitor and its dose were chosen by the investigators in Val-HeFT and CHARM-Added. The mean dose of captopril at baseline was about 80 mg in these two CHF trials compared with 107 mg in the combination arm of VALIANT. Although this could be an important difference between the trials, the prespecified “recommended dose of ACE inhibitor” subgroup analysis of CHARM-Added appears to show clear efficacy of candesartan even when large doses of ACE inhibitor were taken in contrast with Val-HeFT, in which greater efficacy of the ARB was reported in patients on the lower ACE inhibitor dose at baseline.<sup>3</sup> In CHARM-Added the effect of candesartan was similar in patients taking no ACE-inhibitor, a moderate dose or a high dose of ACE-inhibitors. These findings support the pharmacologic evidence that ACE inhibitors and ARBs have distinct mechanisms of action and that, clinically, the two classes of drug can complement each other in a way that improves outcomes in patients with heart failure. (Fig. 3)



**Figure 3.** Cardiovascular death or hospital admission for CHF in relation to concomitant treatment at baseline. (Adapted with permission from Granger et al)<sup>15</sup>

When 50 mg of losartan daily was compared with 150 mg of captopril daily in the OPTIMAAL trial, captopril was shown to be superior, and when similar doses of captopril and losartan were compared in patients with moderate-to-severe heart failure in the ELITE II, the results also favored captopril. In contrast, in two recently reported clinical trials in which the investigators were allowed to increase the dose of losartan gradually to 100 mg daily, there was a significant reduction in the incidence of heart failure among high-risk patients; this finding raises the important question of whether higher doses of losartan might have been more effective in reducing the rates of cardiovascular events in the OPTIMAAL trial.<sup>30-32</sup>

During long-term treatment with an ACE inhibitor, RAS escape can occur, possibly because of induction of ACE, conversion of angiotensin II from angiotensin I through enzymatic pathways other than ACE (e.g. chymase) or both.<sup>3</sup> In a large number of CHF patients elevated Ang II levels were found despite treatment with maximally recommended doses of ACE inhibitors.<sup>33</sup> In Val-HeFT and especially CHARM-Added (76% of the patients in NYHA functional class III/IV compared with 38% in Val-HeFT), ARB treatment was started in patients who were persistently symptomatic despite receiving long-term ACE inhibitor treatment and who probably had chronic activation of the RAS. Consequently, adding an ARB to an ACE inhibitor might bring an incremental clinical benefit.<sup>3</sup>

Even dual RAS blockade did not reduce all-cause mortality or cardiovascular mortality or the rate of secondary end-points compared with captopril or valsartan alone in the VALIANT trial, a post hoc analysis in this study showed that dual RAS blockade resulted in a reduction in the cumulative rate of admission for recurrent MI or heart failure.<sup>11,30</sup>

Another important question is whether the effects of valsartan can be interpreted as a “class effect” of ARBs. There are obvious differences in pharmacologic profiles among the ARBs but the most convincing argument not to make assumptions regarding class effects is underscored by the different clinical outcomes in the OPTIMAAL and VALIANT trials, in which the determination of the correct dose of an angiotensin-receptor antagonist became a matter of life and death.<sup>30</sup>

Heart failure with preserved LV systolic function has become a clinical entity during the last decade. In CHARM-Preserved trial, candesartan did not lead to a significant reduction in the primary outcome, although there was a substantial and significant reduction in heart failure hospitalization. The role of ARBs in CHF with preserved LV systolic function remains uncertain, and no ARB has yet been approved to treat these patients. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study is an ongoing placebo-controlled trial assessing the efficacy of irbesartan in reducing death or cardiovascular hospitalization in symptomatic patients with CHF and LVEF > 45%; data from this trial are awaited with great interest.<sup>34</sup>

## CONCLUSIONS

ARBs have earned their place among the therapies that can reduce cardiovascular mortality

and morbidity in patients with high-risk MI and in patients with CHF.

The dual RAS blockade has proved its beneficial effect on the improvement of the LV function. The addition of ARBs to the standard therapy with ACE inhibitor and beta-blocker (triple therapy) increases LVEF, without increasing all-cause mortality, cardiovascular mortality and morbidity.

The low mortality exhibited by patients treated for heart failure with ACE inhibitors and/or ARBs plus beta-blockers makes mortality an unlikely candidate end-point for future studies. Quality of life assessment, hospitalizations specifically for heart failure, LV structure and neurohormonal measurements appear to be useful markers, eventually incorporated in composite scores to determine efficacy.

The 2005 revision of ESC-CHF guidelines recommends adding an ARB in patient with CHF and LVEF who remained symptomatic despite treatment with an ACE inhibitor and a beta-blocker in order to reduce mortality and hospital admission for worsening heart failure.

Although recent trials failed to demonstrate an incremental clinical benefit of dual RAS blockade in acute MI, compared to the respective monotherapies, strong experimental data sustain that association between ARBs and ACE inhibitors is better than either therapy alone in preventing LV remodeling after acute MI and its progression to heart failure.

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