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Scientific Update™

The Emerging Role of Angiotensin Receptor Blockers in Cardiovascular Protection: New Data, New Studies

A Report on Recent Presentations, including a Satellite Symposium, at the 24th Congress of the European Society of Cardiology

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Activation of the renin-angiotensin-aldosterone system (RAAS) contributes significantly to clinical progression in the cardiovascular (CV) continuum, from mediating the effects of risk factors such as diabetes and hypertension, to contributing to organ damage including renal failure, coronary artery disease (CAD), myocardial infarction (MI), heart failure, and ultimately death. Pharmacologic agents that modulate RAAS activation have been tested at several points in the CV continuum. Recently, type-1 angiotensin receptor blockers (ARBs) have been shown to improve different types of clinical outcomes in patients with diabetes, hypertension, and heart failure. The use of ARBs at various stages of the CV continuum is one of the most rapidly evolving areas of CV research. Although the therapeutic role of ARBs has been addressed in previous issues of *Cardiology Scientific Update*, due to rapid developments in this area, this issue will focus on a discussion of recently presented trials, as well as ongoing trials, on the use of ARBs along the CV continuum.

Prevention of diabetes and its complications

The prevalence of diabetes mellitus is rapidly increasing worldwide and is currently estimated to affect more than 7% of the US population.[1] Diabetes, type-2 diabetes in particular, is now one of the most frequent causes of end-stage renal disease (ESRD).[2] In the natural history of diabetic nephropathy, the earliest clinical evidence of nephropathy is the appearance of low, but nonetheless, abnormal levels of albumin in the urine (≥ 30 mg/day), referred to as microalbuminuria. Accordingly, studies that address interventions to favourably alter the natural history of diabetic nephropathy would involve the assessment of interventions on microalbuminuria, in addition to progression to renal failure.

Microalbuminuria

Two studies have examined the effect of ARBs on microalbuminuria in patients with type-2 diabetes.

- The IRbesartan MicroAlbuminuria (IRMA-2) trial demonstrated that the ARB irbesartan, when compared to placebo, delayed the progression of microalbuminuria to clinical proteinuria in type-2 diabetes.[3]
- The MicroAlbuminuria Reduction with VALsartan (MARVAL) trial[4] differed from IRMA-2 in that it was designed to test the hypothesis that an ARB can reduce microalbuminuria *independently* of its blood pressure lowering effect. Three hundred and thirty-two patients with type-2 diabetes were randomized to receive either valsartan 80 mg daily or amlodipine 5 mg daily over 24 weeks with a target blood pressure of 135/85 mm Hg. The reduction in the urinary albumin excretion rate (UAER) and the percentage of patients

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who returned to normal albuminuric status were greater in the valsartan-treated group (30% for valsartan vs. 15% for amlodipine), despite equivalent lowering of blood pressure.

Diabetic nephropathy

Both the Irbesartan Diabetic Nephropathy Trial (IDNT)[5] and the Reduction in Endpoint in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study[6] were powered to detect an approximately 25% difference in primary outcome measures, a doubling of baseline serum creatinine, progression to ESRD, or death, between the test drug and placebo. IDNT had 3 treatment arms: placebo, amlodipine, and irbesartan. In both IDNT and RENAAL, there was a significant 20% and 16% reduction, respectively, in patients reaching the primary endpoint compared to placebo, despite similar reductions in blood pressure.

Based on current findings, at least two questions remain unanswered. First, are the IDNT and RENAAL results a class effect? Second, are ARBs equivalent to ACE inhibitors in patients with diabetic nephropathy? There are, as yet, no definitive answers to these questions, although to address the second question, it is worthwhile to cite a small study conducted in Canada.[7] In this study, 122 patients with type-2 diabetes and microalbuminuria were randomized to treatment with placebo, valsartan, and captopril for 1 year. At the end of the year, the change in UAER relative to placebo was similar for the valsartan (-46%) and the captopril group (-45%).

Prevention of diabetes

The metabolic syndrome has been increasing in epidemic proportions, setting the stage for both diabetes and CV disease. A common mechanism may be the production of adipokines by fat tissue. This may contribute to the elevation of highly sensitive C-reactive protein levels, which in turn predisposes to development of atherosclerotic events *and* insulin resistance. Insulin resistance progresses from hyperinsulinemia, to the metabolic syndrome, on to glucose intolerance, and finally frank diabetes.[8] This progression parallels the progression of endothelial dysfunction associated with vascular inflammation, thrombosis and oxidative stress, and atherosclerosis and vascular events. Fortunately, this progression may involve a prolonged period and strategies to prevent type-2 diabetes are therefore potentially feasible. Both low insulin secretion and increased insulin resistance strongly predict the development of type-2 diabetes.[9] ARBs improve endothelial function,[10] insulin sensitivity,[11] and have recently been shown to reduce vascular events and new-onset diabetes in high-risk hypertensives, at least when compared to a ß-blocker.[12] Accordingly, a reasonable hypothesis is that increasing insulin secretion and improving endothelial function may prevent or delay the onset of diabetes.

The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) trial was therefore designed to test this hypothesis. Seven thousand five hundred patients with known impaired glucose intolerance will be randomized in a 2 x 2 factorial design to nateglinide (a short-acting insulin secretagogue that lowers postprandial insulin and glucose without inducing hypoglycemia),[13] the ARB valsartan, or matching placebo. All subjects will receive the same lifestyle advice. The primary endpoints include progression to diabetes at 54 months and composite CV events at 69 months. The study was launched in November 2001. NAVIGATOR will be the largest diabetes prevention trial to date and is also the only one that may demonstrate reduction in CV events.

Treating high-risk hypertensive patients

The ideal antihypertensive drug should not only normalize blood pressure, it should also reduce associated CV morbidity and mortality. The role of the RAAS in hypertension and its complications is well-defined.[14]

The recently published Losartan Intervention For Endpoint reduction in hypertension study (LIFE) is the first large-scale mortality-morbidity trial of an ARB in hypertension. In LIFE, 9,193 patients, 55-80 years of age with essential hypertension (mean blood pressure 174/98 mm Hg) with electrocardiographic evidence of left ventricular hypertrophy (LVH) were assigned losartan- or atenolol-based therapy for at least 4 years. The ARB losartan exerted beneficial effects on the composite CV endpoint that included cardiovascular death, nonfatal MI, and nonfatal stroke (-13%, P=0.021) over those of the ß-blocker atenolol, above and beyond that of lowering blood pressure.[12] However, for the diabetic subgroup, the beneficial CV effects of losartan were driven primarily by a 25% reduction in stroke, with no significant benefits observed in CV deaths and MI. A similar pattern was also observed in the recently published prespecified subgroup analysis of patients with isolated systolic hypertension and LVH.[15,16]

Interestingly, the recently presented Study of Cognition and Prognosis in the Elderly (SCOPE) trial reported similar trends in *elderly* patients with hypertension (ie, beneficial effects primarily attributed to stroke reduction, with no significant benefits observed in CV deaths and MI). The results of SCOPE are not yet published and the interpretation is confounded by a change in protocol in the placebo group.

While the results of LIFE and SCOPE are important, they leave a number of issues unresolved. The key issue in LIFE is the observation that in the entire cohort, losartan significantly

reduced the incidence of stroke, but had no impact on CV death and MI.[12] The reasons for this apparent paradox are unclear. Although conjectural, it is possible that in the LIFE study, the ARB losartan and the ß-blocker atenolol *both* exerted a CV protective effect, but through *different* mechanisms. Thus, the ARB losartan might have exerted a vascular protective effect via antitrophic mechanisms since there was evidence that it had a more superior effect on the regression of LV mass than atenolol.[17] On the other hand, atenolol might have exerted cardioprotection via mechanisms such as antiarrhythmic effects and reductions in heart rate and cardiac work, mechanisms commonly associated with the benefits of ß-blockade in MI and heart failure. The mechanisms underlying the difference in strokes between the losartan and atenolol groups are equally unclear. Broadly speaking, this difference may either reflect an overwhelmingly favourable effect with angiotensin receptor blockade, or a relative lack of effect or even an unfavourable effect of ß-blockade, on vascular structure and endothelial function.[18]

The VALUE study

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial is comparing the ARB valsartan and the calcium channel blocker amlodipine in hypertensives aged ≥ 50 years with a *high-risk CV profile*. The primary hypothesis of VALUE is that for the same level of blood pressure lowering, valsartan will be superior to amlodipine in reducing cardiac endpoints in high-risk hypertensives. The rationale and design of VALUE has been published previously,[19] while the baseline characteristics of the patients were reported more recently.[20]

In brief, between January 1998 and December 1999, 15,314 patients in 31 countries were randomized. Mean blood pressure was 154.7/87.5 mm Hg. Mean age was 67.2 years. Risk factors included coronary heart disease (45.8%), high cholesterol (33.0%), type-2 diabetes mellitus (31.7%), and smoking (24.0%). The primary endpoint is a composite of cardiac morbidity and mortality, including clinically evident or aborted MI by thrombolysis or revascularization, hospitalization for heart failure, and death caused by MI, heart failure, or sudden death. The targeted number of patients expected to reach the primary outcome is 1450. The study is 90% powered to detect a 15% reduction (12.5% in the amlodipine group to 10.63% in the valsartan group) in the primary outcome.

VALUE will address several issues that might not have been addressed by the LIFE study. In contrast to a ß-blocker, the calcium channel blocker amlodipine (besides effectively reducing blood pressure) has no antiarrhythmic properties, does not reduce heart rate, and is not generally considered cardioprotective. Therefore, the VALUE study will have a higher likelihood than the LIFE study in proving the hypothesis that an ARB will reduce cardiac events. Furthermore, the fact that a calcium channel blocker (amlodipine) improves vascular structure and endothelial function more than the ß-blocker (atenolol)[18] will provide insights into the mechanisms for the difference in strokes observed in LIFE.

Secondary prevention post-acute MI

Survivors of an acute MI, particularly those with LV systolic dysfunction and/or clinical heart failure, are at high risk for recurrent adverse clinical events. It has been shown that the ACE inhibitors convincingly reduce mortality in patients post-MI,[21] with the greatest benefits being observed in high-risk patients as described above.[22] However, ACE inhibitors may not block the RAAS completely.[23] Furthermore, a significant number of patients do not tolerate ACE inhibitors because of cough.[24] Accordingly, use of an ARB or an ARB combined with an ACE inhibitor is a potentially attractive alternative strategy. However, in order to use this combination, one needs to prove that an ARB is superior, or at least equivalent, to the gold standard ACE inhibitor in high-risk post-MI patients. Two studies have been conducted to address this question.

The OPTIMAAL study

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) randomized 5477 patients with acute MI and clinical signs of heart failure and/or systolic LV dysfunction and/or new anterior Q-wave MI to the ACE inhibitor captopril (50 mg tid) or the ARB losartan (50 mg daily). The primary outcome was all-cause mortality. The study was designed to test for superiority and non-inferiority of losartan over captopril, with a 95% power to detect a 20% difference in primary outcome favouring losartan. The non-inferiority margin was 10%. Results of the OPTIMAAL trial were recently presented and published.[25] A total of 937 deaths occurred. For this primary outcome, the point estimate favoured captopril (RR 1.13, 95% CI, 0.99 - 1.28, *P*=0.069). Because the upper limit of the 95% CI exceeded 1.10, losartan was neither "superior" nor "non-inferior" to captopril. Many investigators believe that the dose of losartan employed was too low to permit a fair comparison of losartan and captopril. Based on current published results, the OPTIMAAL study cannot conclusively address the role of ARBs in the management of patients post-MI. Therefore, losartan cannot be generally recommended in this population and ACE inhibitors should remain the first choice therapy in patients after complicated acute MI.[25]

Table 1: Comparison of the design of the OPTIMAAL and the VALIANT study		
	OPTIMAAL	**VALIANT**
Comparison	Losartan 50 mg/d vs. captopril 150 mg/d	Valsartan 320 mg/d vs. valsartan160 mg/d + captopril 150 mg/d vs. captopril 150 mg/d
Sample size	5477	14809
Study population	Age ≥ 50, MI with HF, or MI with LVEF < 35% or LVEDD > 65 mm and/or new Q-wave anterior MI or new LBBB or reinfarction with prior anterior MI	MI with radiographic or clinical evidence of HF, or LV dysfunction (SAVE, AIRE and TRACE criteria)
Target event	937 deaths	2700 deaths
Study power (test for superiority)	95% power to detect a 20% reduction in mortality by losartan compared to captopril	95% power to detect a 17.5% reduction in mortality, 86% power to detect a 15% reduction in mortality with either use of valsartan compared to captopril
Study power (test for Non-inferiority)	Upper one-sided 95% boundary for hazard ratio (losartan versus captopril), 1.10	74% power if equivalent, 88% power if valsartan is 2.5% better than captopril

HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction

The VALIANT study

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) differs in many aspects from the OPTIMAAL trial. Details of the rationale and design of OPTIMAAL and VALIANT have been published recently.[26,27] A comparison of the study design of OPTIMAAL and VALIANT is summarized in Table 1.

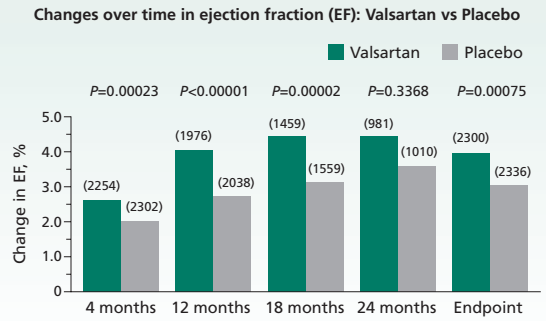
- First, to test for the superiority hypothesis, the VALIANT study has the power to detect a more realistic and yet clinically important 15% reduction in mortality.
- Second, to test the non-inferiority hypothesis, the study prospectively defines a margin for making a non-inferiority comparison that has adequate statistical power to test whether the use of valsartan, if not different from captopril, could be considered comparable (and therefore superior than placebo). This is one of the most important questions that clinicians want to know.
- Third, the study is equally weighted to compare ARB versus ACE inhibitor therapy, as well as combination therapy of ARB and ACE inhibitor, and ACE inhibitor alone.
- Fourth, more patients in VALIANT than in OPTIMAAL have diabetes (23.1% versus 16.9%) and prior MI (27.9% versus 18.1%), suggesting that patients may have higher risk.
- Finally, in VALIANT, 50% of the patients received reperfusion therapy and 70% received ß-blockade therapy, reflecting contemporary management of MI.

In summary, the magnitude and design of VALIANT will enable it to detect even small differences between ACE inhibitor and ARB therapy and also study the addition of high-dose valsartan to the proven dose of an ACE inhibitor. As a result, VALIANT will likely provide definitive answers about the use of these agents in high-risk patients post-MI.

Treatment of heart failure

There have been two studies that have assessed the effect of an ARB on clinical outcomes in patients with heart failure. Results of the Losartan Heart Failure Survival (ELITE II) study,[28] comparing losartan and captopril, were inconclusive and the study had limitations similar to those described in the OPTIMAAL study. The Valsartan Heart Failure Trial (Val-HeFT), on the other hand, was a placebo-controlled trial of valsartan in 5010 patients with background therapy of ACE inhibitors.[29] Results of the main Val-HeFT trial, as well as the subgroup analysis of patients who were not on background therapy of ACE inhibitors, have been reviewed in previous issues of *Cardiology Scientific Update*. In brief, when compared to placebo (ie, already on optimal therapy with ACE inhibitor), valsartan had no effect on all-cause mortality,

Figure 1: Val-HeFT echocardiographic data



the first primary endpoint, but reduced combined mortality and morbidity, the second prespecified primary endpoint, by 13.2%, that was driven almost exclusively by a 25% reduction in heart failure hospitalization. In the subgroup analysis of the 366 patients (7.3%) who were *not on* ACE inhibitors at baseline, valsartan reduced all-cause mortality by 33.1%, morbidity by 44.4%, and heart failure hospitalizations by 56.4%. In the subgroup of 794 patients who were *on* both ACE inhibitors and ß-blockers at baseline, however, valsartan increased all-cause mortality ($P = 0.09$), with a trend for increased combined mortality and morbidity ($P = 0.10$).

New data on Val-HeFT

The Val-HeFT study has a large body of data, including echocardiographic and neurohormonal measurements, that may provide mechanistic insights into the main observations of the trial and further define the role of ARBs in the treatment of heart failure. Echocardiographic data from the Val-HeFT study were recently presented and published.[30] Data on left ventricular ejection fraction (LVEF) are shown in Figure 1. At all time points throughout the study, the valsartan group had significantly greater increases in LVEF compared to the placebo group. On the other hand, the decreases in left ventricular end-diastolic diameter (LVEDD) were significantly greater in the valsartan group. Importantly, in the subgroup of patients on baseline therapy with both ACE inhibitors and ß-blockers, there were no significant differences between the valsartan and placebo groups in the changes in LVEF and LVEDD. This suggests that there was no biologic explanation for an adverse interaction between ACE inhibitors, ß-blockers, and valsartan, at least based on LV function and remodeling.

Val-HeFT is a study with the largest neurohormone database to date. Preliminary data presented at recent scientific meetings have demonstrated that valsartan signif-

Figure 2: Outcomes trials of angiotensin receptor blockers in the cardiovascular continuum

Diabetes and complications	Hypertension and CV risks	CAD and MI	Heart Failure
NAVIGATOR (valsartan)	LIFE (losartan)		
RENAAL (losartan)	SCOPE (candesartan)	Val-PREST (valsartan)	ELITE II (losartan)
IDNT (irbesartan)	**VALUE** (valsartan)	OPTIMAAL (losartan)	Val-HeFT (valsartan)
IRMA-II (irbesartan)	**ONTARGET/ TRASCEND** (telmisartan)	**VALIANT** (valsartan)	**CHARM** (candesartan)
MARVAL (valsartan)			

Ongoing trials are in bold letters

icantly reduced brain natriuretic peptide (BNP) levels and attenuated the increase in plasma norepinephrine levels observed in the placebo group.[31] In the subgroup of patients who were on both ACE inhibitors and ß-blockers, the observations on plasma norepinephrine and BNP were directionally similar to the overall group, although the differences were not significant. These data therefore indicate again that there was no biologic explanation for an adverse interaction between ACE inhibitors, ß-blockers, and valsartan, at least based on changes in plasma norepinephrine and BNP levels. Similar conclusions were drawn based on subgroup analysis of heart failure hospitalization. Indeed, the annualized mortality rate of the subgroup of patients on ACE inhibitors and ß-blockers was only 6%. It would conceivably be very difficult to improve mortality further in this group of patients. Finally, the decline in systolic blood pressure was similar (ie, 4 mm Hg) in the 4 subgroups.

Results of Val-HeFT indicate that valsartan improves morbidity in patients with heart failure. This effect is most pronounced in patients who are not on ACE inhibitors. The new data on LV function, hospitalization, and neurohormonal measurements do not provide mechanistic support for an adverse interaction between ACE inhibitors, ß-blockers, and valsartan. Results of the VALIANT study, which will be available soon, will help resolve this issue.

Summary

In summary, the role of ARBs in the treatment of CV disease is rapidly evolving as the results of large-scale outcomes trials are reported. Completed and ongoing trials are shown in Figure 2. As shown, they cover almost the entire spectrum of the CV continuum, from prevention to end-stage disease. Besides providing evidence that will have an impact on clinical practice, these studies will

also provide mechanistic information that will help investigators gain a greater understanding of the role of angiotensin II on progression on the CV continuum.

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