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Inhibition of the renin-angiotensin system, with particular reference to dual blockade treatment

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Background

The presence of diabetes profoundly increases the risk of developing cardiovascular disease, largely because of the adverse combination with hypertension.¹

Hypertensive, diabetic patients carry a two-fold increase of developing cardiovascular complications compared with non-diabetics.²

Modulation of the renin-angiotensin system (RAS) has become essential in treating hypertension and delaying the onset of diabetic nephropathy. Since the 1980s, numerous studies have shown that the use of angiotensin-converting enzyme inhibitors (ACE-I) has beneficial effects when treating hypertension and renal disease in diabetes, as well as non-diabetic renal disease.³⁻⁴

Tight blood pressure (BP) control has become essential for this group of patients and the benefits are undisputed. The UKPDS study showed a 24% risk reduction among Type 2 diabetics in whom BP was reduced to below 150/85 mmHg over a study period of eight years.⁵ The HOT study showed significant risk reduction in cardiovascular events in diabetics in whom diastolic BP was reduced to approximately 80 mmHg (mean BP 144/81 mmHg). A remarkable proportion of this particular patient group was treated with an ACE-I.⁶

ACE inhibition alone is not always able to provide a satisfactory treatment strategy for the individual patient. Either insufficient BP control or continued microalbuminuria may prevail in spite of high doses of ACE-I; this has created interest in alternative ways of inhibiting the RAS.

There are several reasons for optimising RAS blockade. During long-term ACE-I treatment, the phenomenon of 'ACE-escape' develops.^{7,8} It seems that plasma levels of angiotensin II (Ang II) and aldosterone may return to pre-treatment levels, which may induce incessant progression of nephropathy and chronic heart failure.

In chronic heart failure patients, the angiotensin AT₁-receptor blocker (ARB), valsartan, was added to the maximum recommended dose of ACE-I (40 mg of long-acting ACE-I) and significantly reduced the BP response to infused Ang II, even though the high-dose ACE-I had been given for over three months.⁹

This could be due to the fact that ACE-I do not completely block the conversion of angiotensin I (Ang I) to Ang II.

Alternative pathways of converting Ang I to Ang II are of great influence, especially in the failing

heart, kidneys and large resistance vessels.¹⁰⁻¹³ The chymase, cathepsin and serine protease-inhibitable conversion of Ang I to Ang II appear to be activated in disorders in which high levels of oxidative stress are present, such as vascular pro-inflammatory processes, atherogenesis and diabetes.^{14,15} In these circumstances, up to 60-70% of circulating Ang II may be produced by alternative pathways.¹⁶

Finally, tissue ACE activity, which is found in lung, blood vessels, myocardium and in the kidneys,^{17,18} has been proposed to mediate more long-term tissue effects, such as glomerular hypertrophy and left ventricular remodelling.^{19,20} This is of utmost importance, since tissue ACE activity is not always sufficiently blocked by regular doses of ACE-I, and also because the 'ACE-escape' mechanism returns plasma levels of Ang II to normal, so that tissue-ACE activity becomes uncontrolled at the level of the AT₁ and AT₂ receptors.²¹

The obvious purpose of using dual blockade treatment (combining an ACE-I and an ARB) is to counteract the above-mentioned mechanisms. By dual blockade treatment, it might be possible to obtain a more complete inhibition of the RAS and thus vastly enhance the desired therapeutic effect. Dual blockade might also be able to block the effects of both non-ACE pathways and tissue-ACE activity, since both ACE and the AT₁-receptor are inhibited simultaneously, thereby increasing bradykinin levels.

It seems obvious to apply this treatment to conditions known to be characterised by an activated RAS cascade, such as hypertension, heart failure and nephropathy in both diabetics and non-diabetics.

The following paper presents an overview of the latest trials concerning attenuation of the RAS with special emphasis on the use of dual blockade in the above-mentioned conditions.

Hypertension

In 1995, Azizi *et al.* demonstrated an additive effect on BP and renin of single doses of losartan combined with captopril in a group of mildly sodium-depleted normotensive volunteers.²² Similar results were found by the same research group in 177 patients with essential hypertension treated with enalapril, 20 mg, or losartan, 50 mg, or the combination of both drugs, over a six-week period. The combination therapy was slightly more effective on clinic diastolic BP (DBP) compared with losartan (3.2 mmHg) and was also

Table 1 Results of trials of dual RAS blockade on blood pressure.

Trial	Population	Study drug	n	Blood pressure lowering systolic/diastolic mmHg
ACTION ²⁷	Essential hypertension	Candesartan 16–32 mg/ACE-I	473	13.4/4.3
Azizi <i>et al.</i> ²²	Essential hypertension	Losartan 50 mg/Enalapril 10 mg	177	3.4/3.6
CALM ²⁸	Hypertensive, microalbuminuric diabetics	Lisinopril 20 mg/Candesartan 16 mg	199	10.0/6.0
Kincaid-Smith ³⁶	Normotensive nephropathy	Candesartan 8 mg/ACE-I	60	6.0/2.0
Rossing <i>et al.</i> ³⁸	Diabetic nephropathy	Candesartan 8 mg/ACE-I	18	10/- *
RESOLVD ⁵⁰	Chronic heart failure	Candesartan 4–8 mg/Enalapril	332	6.5/3.8
Ruilope <i>et al.</i> ²⁹	Chronic heart failure	Valsartan 160 mg/Benazepril 10 mg	86	21.5/13.0
V-HEFT ⁴⁸	Chronic heart failure	Valsartan 80–160 mg/ACE-I	55	11/- *

* Diastolic blood pressure was not assessed.

more effective than enalapril (4.0 mmHg). In the same study, in a subgroup of 28 patients, plasma renin activity and Ang I levels were measured. Renin and Ang I levels during the dual blockade treatment were higher, indicating a more profound inhibition of the RAS.²³

In a small trial comprising nine patients, Fagard and colleagues found significantly better BP reduction with enalapril, 20 mg, compared with losartan, 50 mg, but did not find additive effects when the two drugs were combined.²⁴

It is possible that these rather modest results relate primarily to the short follow-up period. The full BP-lowering effect of an ARB is fully evident only after 4–6 weeks treatment²⁵ and BP endpoints should probably not be assessed until after this period. In addition, it seems that the losartan dosage of 50 mg may be too small and that 100 mg would facilitate better BP control.²⁶

Several recent studies have shown evidence of efficient BP control with longer follow-up and higher dosages of ARB.

In a large, open-label trial, including 6465 hypertensive patients, doses of 16–32 mg of candesartan were added to either concomitant anti-hypertensive treatment or used as monotherapy. In all treatment arms, BP was significantly lowered over a period of eight weeks. Patients in the dual blockade treatment group did not achieve any additional reduction in BP, compared with a combination of candesartan and diuretics or beta-blocker.²⁷

In the CALM study, Type 2 diabetics with microalbuminuria and hypertension were treated with either lisinopril 20 mg o.d., candesartan 16 mg o.d. or both drugs in combination. Patients were primarily treated with lisinopril or candesartan and after 12 weeks of treatment, patients continued with either monotherapy or dual blockade for an additional 12 weeks. There was no difference in BP between the lisinopril and candesartan groups in the first 12 weeks of treatment but the

group taking combination therapy obtained significantly greater BP reduction compared with the other treatment regimens in the following period.

The largest difference in arterial BP (11.2 mmHg) was found when comparing the combination of lisinopril and candesartan with candesartan alone.

The trial also found a significant reduction in urine albumine creatinine ration (UACR) with combination treatment, compared with both lisinopril and candesartan. However, since BP was also significantly lower in the combination treatment group, it could not be determined whether this was a consequence of improved BP control.²⁸

Table 1 shows doses and overall BP-lowering effects of dual blockade trials mentioned in this article.

No large studies of dual RAS blockade are currently underway, though both the LIFE and the VALUE trials will contribute valuable information about ARB treatment in high-risk hypertensive patients.^{29,30}

Nephropathy

In terms of treating both non-diabetic and diabetic nephropathy with dual RAS blockade, recent trials with ARBs have suggested that efficient blockade of the RAS improves renoprotection.

Four large-scale trials have shown that ARBs provide a renoprotective effect, reducing morbidity independent of BP reduction in Type 2 diabetics with nephropathy.

The RENAAL trial (Reduction of endpoints in Non-insulin dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) included 1513 patients with Type 2 diabetes, proteinuria and elevated serum creatinine. Patients were treated with losartan, 50 or 100 mg. During a 3.6-year follow-up period, a significant 28% reduction in end-stage renal disease was demonstrated.³¹

In the IDNT trial, 1713 hypertensive, Type 2 diabetics were randomised to receive either irbe-

Table 2 Trials with AT₁-receptor blockers in Type 2 diabetics with nephropathy.

Trial	Study drug	No. of patients	Follow-up period	Endpoints	Result
RENAAL ³¹	Losartan 50 and 100 mg	1513	3.6 years	ESRD Doubling of inclusion S-creatinine value Death	28% RR reduction 25% RR reduction Non-significant
IDNT ³²	Irbesartan 75–300 mg Amlodipine 2.5–10 mg	1715	2.5 years	Composite endpoint including, ESRD, death, doubling of inclusion S-creatinine value	33% RR reduction compared to placebo 37% RR reduction compared to amlodipine
IRMA 2 ³⁴	Add-on treatment of Irbesartan 150–300 mg	590	2 years	Progression to overt proteinuria	70% reduction
MARVAL ³³	Valsartan 80 mg Amlodipine 5 mg	332	24 weeks	UAER (mcg/min)	Significantly better reduction with Valsartan

No patients were treated with both ACE-inhibitor and the test-drug.

sartan, 75–300 mg o.d., the calcium channel blocker, amlodipine, 2.5–10 mg o.d., or placebo.

Both irbesartan and amlodipine were titrated to the maximum tolerated dose.

All patients had manifest nephropathy, with albuminuria of ≥ 900 mg/24-hour and serum creatinine levels of 106–265 $\mu\text{mol/L}$ among males and 88–265 $\mu\text{mol/L}$ among the female population.

After a 2.5-year follow-up period, the composite endpoint of end-stage renal disease, death, and doubling of inclusion serum-creatinine value was significantly reduced in the irbesartan group, compared with both amlodipine and placebo, suggesting a specific renoprotective effect of the ARB which was independent of its ability to lower BP.³²

The same result was found in the MARVAL trial, in which 332 Type 2 diabetics were treated with either Valsartan (80 mg) or amlodipine (5 mg) for 24 weeks. The target BP was 130/85 mmHg, which was achieved through dose-doubling or addition of either a thiazide or alpha-blocker. Urine albumine excretion rate (UAER) was significantly reduced by valsartan.³³

Finally, the IRMA II trial (Irbesartan Microalbuminuria Type 2 diabetes mellitus in hypertensive patients) randomised 590 Type 2 diabetics with hypertension and microalbuminuria to receive either irbesartan (150–300 mg daily) or placebo, added to their usual hypertensive therapy (though ACE-I were excluded).

The primary endpoint was progression to overt proteinuria, which was significantly reduced in the irbesartan group by 70%.³⁴

It seems, though, that all trials used high-dose ARBs to achieve significant reduction in endpoints. However, since none of the results of these trials have yet been published, it is too early to draw any final conclusions from them over the optimum treatment of diabetic nephropathy. Overall results from these trials are displayed in Table 2.

Only small trials using dual blockade have given results which are available at the present

time. In non-diabetic patients, three trials are currently available.

In a small trial, eight patients with biopsy-verified IgA nephritis and massive proteinuria (1–3 g/24-hour), were treated with losartan (50 mg) added to ACE inhibition. Proteinuria was reduced over four weeks to a mean of 0.5 g per day. This was significantly lower than either ACE-I or losartan alone.³⁵

Kincaid-Smith and co-workers found significantly reduced proteinuria in normotensive patients with renal disease when candesartan (8 mg) was added to concomitant ACE-I treatment.³⁶

Finally, Ruilope *et al.* treated 108 patients with chronic renal failure in a three-arm design. One group received valsartan, 160 mg o.d., a second group received valsartan, 80 mg, and 5 to 10 mg benazepril, while a third group received 160 mg of valsartan and 5 to 10 mg benazepril. Dual blockade was given for four weeks. Systolic BP was significantly lowered in both dual blockade treatment groups. Diastolic BP was significantly lowered in all three treatment groups. Proteinuria was only significantly reduced in the dual blockade regimen with high-dosage valsartan.³⁸

In a small series of only seven patients with diabetic nephropathy, BP was significantly lowered when losartan was added to ACE-inhibition treatment, though proteinuria was not reduced significantly.³⁷ This was obtained in another small trial including Type 2 diabetics with nephropathy. During a 2-month period in a double cross-over design, candesartan, 8 mg, was added to concomitant ACE-I treatment. During the follow-up period both albuminuria and BP was significantly reduced.³⁹

Congestive heart failure

Activation of the neurohumeral systems in heart failure and the stimulation of tissue-ACE activity in the failing heart muscle contributes to the high morbidity and mortality among heart failure patients.

These mechanisms, in particular Ang II, are believed to be major determinants in left ventricular remodelling and induction of hypertrophy, fibrosis and apoptosis in the failing heart.^{40,41} Modulation of these neurohumeral systems has successfully lowered morbidity and improved survival for this group of patients.⁴²⁻⁴⁶

The role of addition of ARBs to existing heart failure treatment has not yet been fully established. The recently published ELITE-II trial was unable to show any benefit of losartan treatment compared with captopril among 3152 heart failure patients (NYHA II-IV) with a mean follow-up period of 555 days. The primary endpoint of all-cause mortality was not significantly affected, though there was a trend towards greater mortality benefit with captopril.

With respect to these results, the authors suggested that the use of ARBs in heart failure should be restricted to patients who are unable to tolerate ACE-I.⁴⁷

One might question whether the ELITE-II trial selected comparable doses of losartan (50 mg o.d.) and captopril (50 mg t.d.s.). A dosage of 50 mg of losartan may not be sufficient to effectively inhibit the AT₁-receptor, and the dosage should probably be doubled in order to achieve full receptor blockade over a 24-hour period. This could be a reason why this study did not come out in favour of losartan.

Several dual blockade trials in heart failure have shown promising results.

The V-HeFT trial found beneficial effects on both BP, hormonal and haemodynamic factors in a small, short-term, placebo-controlled study in heart failure patients.⁴⁸

Hamroff and colleagues found that exercise capacity in a treadmill exercise significantly improved over a six-month follow-up period when losartan (50 mg) was added to maximally-recommended or tolerated doses of ACE-I in a placebo-controlled study including 33 patients with heart failure.⁴⁹

In addition, the RESOLVD pilot trial found positive results, randomising 768 heart failure patients (NYHA II to IV) to either candesartan (up to 8 mg), or enalapril, or combined candesartan and enalapril. The combination of candesartan and enalapril was more effective in preventing left ventricular remodelling than either candesartan or enalapril alone. Levels of brain-natriuretic-peptide were also significantly reduced during the 43-week follow-up period.⁵⁰

Therefore, it was surprising that the recently published Val-HeFT trial, which was a comprehensive heart failure study using valsartan added to concomitant heart failure medication showed that patients treated with both an ACE-I and an ARB did not benefit from this treatment, and indeed, unexpectedly, that patients treated with both ACE-I, beta-blocker and valsartan had a 10% increase in the combined endpoint of all-cause mortality and morbidity.⁵¹ Even though the study was not designed specifically to investigate dual blockade in heart failure and the above-mentioned results were based on subgroup analysis and so should be interpreted with caution, one must question

whether some precautions should be taken in this specific group of patients.

The issue of using ARBs combined with ACE-I will probably not be resolved until the results of the ongoing major trials (including the CHARM trial with candesartan) are reported.

The CHARM trial (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity), will include approximately 6500 patients with heart failure. The CHARM program consists of three independent, parallel, placebo-controlled studies in patients with

1. left ventricular ejection fraction (LVEF) \leq 40%, ACE-I treated (n=2300);
2. LVEF less than or equal to 40%, ACE-inhibitor intolerant (n=1700);
3. LVEF $>$ 40%, not treated with ACE-I (n=2500).

The three studies will be combined to evaluate the effect of candesartan on all-cause mortality in the broad spectrum of symptomatic heart failure. The study is expected to end in the third quarter of 2002.⁵²

Another study of great interest is also directed towards the VALIANT trial (Valsartan in Acute Myocardial Infarction Trial) which includes 14,500 patients with prior myocardial infarct (MI) and heart failure. The trial is designed with three arms, giving equal statistical consideration to survival comparisons of captopril versus the ARB valsartan, as well as the combination of captopril plus valsartan, compared with a proven effective dose of captopril. Patients will be randomised to receive either captopril (50 mg o.d.), valsartan (160 mg o.d.) or the combination of captopril 50 mg plus valsartan 80 mg o.d. Results are due in 2005.⁵³

Retinopathy

No studies on the effects of dual RAS blockade on retinopathy have yet been published. Evidence of alteration of the RAS in retinopathy with ACE-I or ARBs has not been conclusively provided by clinical trials to date.

The EUCLID study group showed a reduction in the rate of progression of retinopathy in a diabetic population (n=530) treated with lisinopril over two years. However, there was a concomitant significant reduction in BP and microalbuminuria, and after correcting for this, the effect on retinopathy was only of borderline significance.⁵⁴ Control of tissue-ACE activity and ACE activity in small retinal vessels may require high concentrations of ACE-I in the circulation. It is thus possible that high doses of long-acting ACE-I are necessary to impose retinal protection.⁵⁵

Of great interest is a new ARB study, DIRECT (Diabetic Retinopathy Candesartan Trials). Four thousand, five hundred patients will be included in total. The study will include both Type 1 and Type 2 diabetics, treated with either candesartan (16-32 mg) or matching placebo, and follow-up will be for three years. Patients who are hypertensive or microalbuminuric, despite active treatment, will be treated with an ACE-I, so a subgroup of dual-blocked patients must be expected in this large trial. Endpoints will be progression of retinopathy, microalbuminuria and BP.⁵⁶

Table 3 Side-effects in dual RAS blockade trials.

Trial	Study drug	n	Follow-up period	Population	Events /adverse effects	Incidence of adverse events (%)
CALM ²⁸	Lisinopril Candesartan	67	12 weeks	Hypertensive, microalbuminuric diabetics	Hypotension Feeling weak	1.5
Azizi <i>et al.</i> ²²	Losartan/enalapril	60	6 weeks	Essential hypertension	Cough	3.5
	Candesartan added to ACE-I inhibitor	546	8 weeks	Essential hypertension	Hypotension	0.8
Kincaid-Smith ³⁶	Candesartan 8 mg	60	26 weeks	Normotensive nephropathy	Unspecified	5
Hebert <i>et al.</i> ³⁷	Losartan added to ACE-I inhibitor	7	1 week	Diabetic nephropathy	Transient hypotension *	29
Hamroff <i>et al.</i> ⁴⁹	Losartan/maximum dosage ACE-I inhibitor	16	26 weeks	Chronic heart failure	Nausea	6
Fagard <i>et al.</i> ²⁴	Losartan/enalapril	6	6 weeks	Essential hypertension	Cough (experienced before combination treatment)	16.6
RESOLVD ⁵⁰	Candesartan/ enalapril	332	43 weeks	Heart failure	Renal dysfunction	0.6
Ruilope <i>et al.</i> ²⁹	Valsartan/Benalapril	86	5 weeks	Chronic renal failure	Hypotension Hyperkalaemia	0.2 2.5
Russo <i>et al.</i> ³⁵	Losartan/ACE-I inhibitor	8	4 weeks	IgA nephritis	Weakness	25
V-HeFT ⁴⁸	Valsartan/Lisinopril	55	24 weeks	Chronic heart failure	Hypotension	10.9

* Two patients experienced transient hypotension, but completed the trial.

Trial acronyms used

CALM	Candesartan and Lisinopril Microalbuminuria study
LIFE	Losartan Intervention For Endpoint reduction in hypertension
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
IDNT	Irbesartan Type 2 Diabetic Nephropathy Trial
MARVAL	Microalbuminuria Reduction with Valsartan trial
IRMA II	Irbesartan Micro-Albuminuria Type 2 diabetes mellitus in hypertensive patients
VALIANT	Valsartan in Acute myocardial infarction
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
DIRECT	Diabetic RETinopathy Candesartan Trials
Val-HeFT	Valsartan Heart Failure Trial
EUCLID	EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus
ELITE	Evaluation of Losartan In The Elderly
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
V-HeFT	Vasodilator-Heart Failure Trial

Tolerability

It would seem likely that efficient blockage of this essential enzymatic system would be associated with high complication rates. In actual fact, dual blockade seems as safe as monotherapy with either ACE-I or ARBs. ARBs are generally well tolerated, even though it is often necessary to titrate patients to maximum dosage to achieve efficient BP control in monotherapy ARB trials.

Only reversible side-effects have yet been reported. Typical side-effects are cough, malaise, hypotension and hyperkalaemia.

In the CALM trial, five patients were excluded because of dizziness and frailty, (two patients in the lisinopril treatment group, two in the candesartan group and one in the combination group).

In a smaller series of normotensive patients with renal disease (n=60) treated with add-on candesartan (8 mg o.d.), only three patients withdrew from the study because of side-effects, all of which were reversible.³⁵

Table 3 gives an overview of side-effects in dual blockade trials.

Future studies

There are still many unanswered questions awaiting results from large clinical trials such as VALIANT, CHARM and DIRECT. The reference medication is crucial in any future studies. Placebo treatment might not give additional information, since it is well established that both ACE-I and ARBs are effective in treating the mentioned entities. Instead, we need to know whether results with dual blockade can be achieved with higher doses of ACE-I or high-dose ARB alone. Could the combination of calcium-channel blocker and ACE-I give additional improvement in renoprotection and BP control, or should beta-blockers be considered in combination with ACE-I and ARBs?

The Val-HeFT trial showed that the combination of both ARB, ACE-I and beta-blockade increased the combined endpoint by 10%, perhaps implying that a certain degree of neurohumeral activation should be maintained, at least in heart failure patients.

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