Mounting evidence for Angiotensin Receptor Blockers in clinical medicine

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Highlights / Hoogtepunte

- Which angiotensin receptor blockers (ARB's) are available?
- What evidence is available for its clinical efficacy?
- How do ARB's compare with ACE-inhibitors in various clinical settings?

- Watter angiotensien reseptorblokkers (ARB's) is beskikbaar?
- Watter bewyse is daar vir die ARB's se kliniese effektiwiteit?
- Hoe vergelyk die ARB's met die AOE-remmers in verskillende kliniese toestande?.

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INTRODUCTION

The Renin-Angiotensin-Aldosterone System (RAAS) participates in the pathophysiology of systemic hypertension, heart failure and diabetic nephropathy.[1,2] Moreover, excessive activation of the RAAS may increase the risk of cardiovascular morbidity and mortality.[3] Therefore, blocking this system (RAAS) may be expected to reduce cardiovascular morbidity and mortality. There are clear and proven advantages for the ACE-inhibitors, in patients with left ventricular dysfunction, with and without signs of heart failure. Evidence is mounting for clinical efficacy of other drugs blocking this system.

AGENTS THAT BLOCK THE RENIN-ANGIOTENS-I ALDOSTERONE SYSTEM [RAAS]

- Angiotensin-Converting Enzyme Inhibitors (ACE-I).
- AT_1-Receptor Blockers (ARB).
- Aldosterone Antagonists.

The unanswered clinical question currently is: Which is the best way to block the RAAS?

ELEVATED LEVELS OF ANGIOTENSIN II

Inappropriately elevated levels of Angiotensin II significantly contribute to cardiovascular disease by:

A. Cardiovascular system [heart and blood vessels]
- Vasoconstriction
- Hypertrophy
- Remodelling

B. Kidney
- Increased Na^+ and water retention

C. Adrenal gland
- Increase Aldosterone
- Increase Catecholamines

D. Brain
- Increase ADH
- Increase sympathetic stimulation

Inappropriately elevated levels of Angiotensin II are involved in the pathophysiology of most cardiovascular diseases including renal disease.

Angiotensin Receptor Blockers

The currently available compounds all selectively block the Angiotensin Receptor type I and the effects of Angiotensin II are selectively blocked, regardless of whether the Angiotensin II is generated by the ACE-system or via a non-ACE system (e.g. Chymase system). The different types of ARB-blockers block the receptor type I in different ways, but it is uncertain whether this is important clinically. ***See Figure I.***

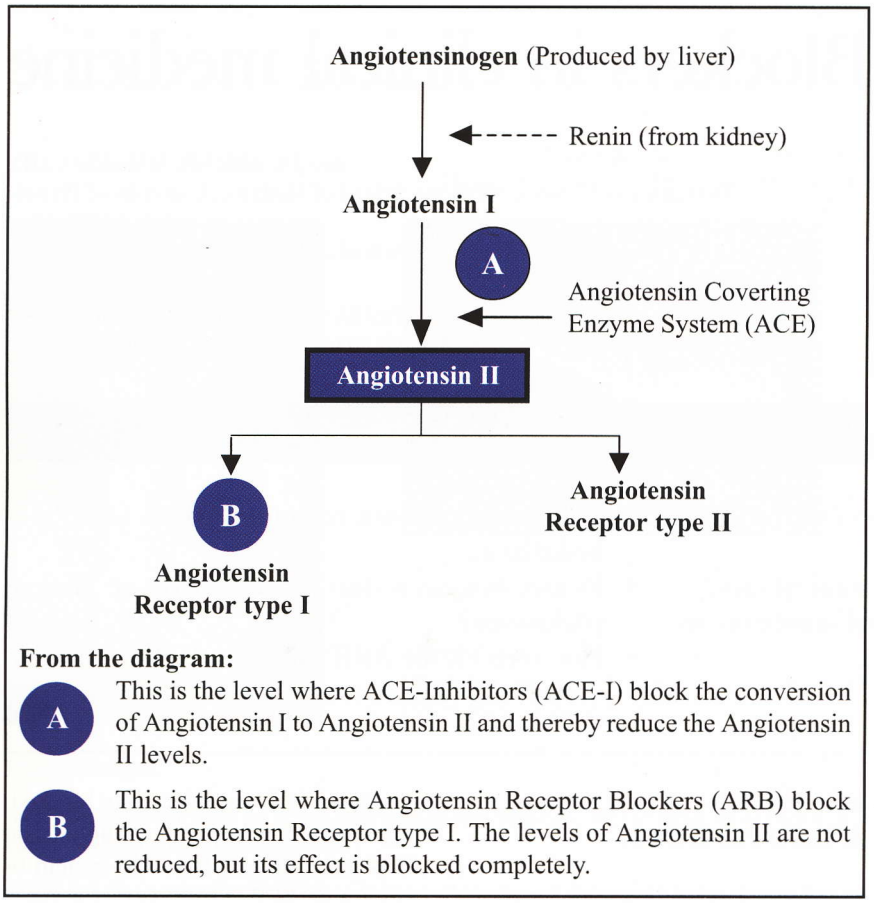
Different Angiotensin Receptor Blockers

- Candesartan (Atacand®)
- Irbesartan (Aprovel®)
- Losartan (Cozaar®)
- Eprosartan
- Telmisartan (Micardis®)
- Valsartan (Diovan®)

The ARB's are unique in that they have ***excellent safety and tolerability profiles***. The side-effect profile and withdrawal rates of ARB's are low, being similar to that of placebo. It is the low side-effect profile and tolerability that make this class of drugs so attractive.

The same safety profile and tolerability have been reported for all the ARB's. However, as with ACE-inhibitors, ARB's should not be prescribed to pregnant women because of toxicity

Figure 1: Physiology of the RAAS
(Renin-Angiotensin-Aldosterone system)



From the diagram:

A This is the level where ACE-Inhibitors (ACE-I) block the conversion of Angiotensin I to Angiotensin II and thereby reduce the Angiotensin II levels.

B This is the level where Angiotensin Receptor Blockers (ARB) block the Angiotensin Receptor type I. The levels of Angiotensin II are not reduced, but its effect is blocked completely.

to the developing foetus. As with ACE-I, ARB should be avoided in patients with renal artery stenosis (fibromuscular dysplasia or atherosclerotic).

I. VASCULAR PROTECTIVE EFFECTS OF ARB'S

A. Ischaemic Heart Disease

Patients with acute myocardial infarction with clinical evidence of heart failure or left ventricular dysfunction have a high morbidity and mortality. ACE-inhibitors improve survival in these patients[4] and are considered essential in the management.

Acute Myocardial Infarction with clinical heart failure

OPTIMAAL-trial

In this trial, 5477 patients with acute MI with heart failure (mean age 55 years) were investigated by comparing losartan vs. captopril for 2.7 years. The results showed a RR 1.13 [95% CI: 0.99-1.28] (p=0.07) not significant for all cause mortality.

Losartan was not more effective than captopril to prevent mortality, but more patients, however, in the captopril group discontinued study medication (23% vs. 17%)[5] due to side effects than losartan.

Valiant

Valsartan in acute MI with heart failure. The result of this trial still needs to be published.

Post-PCI

Post-coronary intervention over 2 years evaluated the use of candesartan vs. placebo. This trial demonstrated a RRR of 51% for revascularisation, non-fatal MI favouring candesartan.

VAL-PREST Trial: reduction of re-stenosis of stent

Valsartan was used over a six-month period to study the effect on restenosis rate after stenting. Two hundred and fifty (250) patients were randomised to valsartan or placebo and coronary angiographic restenosis evaluated at six months. Valsartan (80 mg) reduced stent restenosis rate to 19.2% vs. 38.6% for placebo (p=<0.005). Reintervention rate was 28.7% in placebo and 12.1% in Valsartan (p=<0.005).[7]

B. Cardiovascular disease prevention

The Heart Outcomes Prevention Study (HOPE) provided some evidence that blocking the RAAS with an ACE-Inhibitor can prevent cardiac events in high risk patients.[8] There are, to date, no comparable clinical studies for ARB's for the same indication, but a study with telmesartan ("On-target") is under way.[9] *On-target* also has an arm where the combination of telmisartan and ramipril will be tested to establish whether it can provide a better outcome.

C. Atrial fibrillation

Patients with atrial fibrillation treated with amioderone plus irbesartan had a lower rate of recurrence of atrial fibrillation than did patients treated with amioderone alone.

D. Endothelial function

The physiological role of endothelial function in cardiovascular disease is now well established. The effect of ARB's on endothelial dysfunction and improving NO availability has been demonstrated, but it is not clear if an ARB is better than an ACE-I in restoring endothelial function.

E. Effect of ARB on left ventricular hypertrophy

Meta-analysis of randomised, controlled trials of left ventricular (LV) hypertrophy regression in essential hypertension using various drugs showed that ARB's also reduce LV mass, probably comparable to ACE-I. ***See Figure 2.***

F. Hypertension

Recently the Life-Trial was published investigating the effect of losartan in the treatment of hypertension.

i. LIFE Trial

In this trial, 9193 patients mean age 66.9 years with hypertension and with ECG evidence of left ventricular hypertrophy were treated with losartan vs. atenolol. Hydrochlorothiazide could be added to both groups if necessary to control blood pressure.

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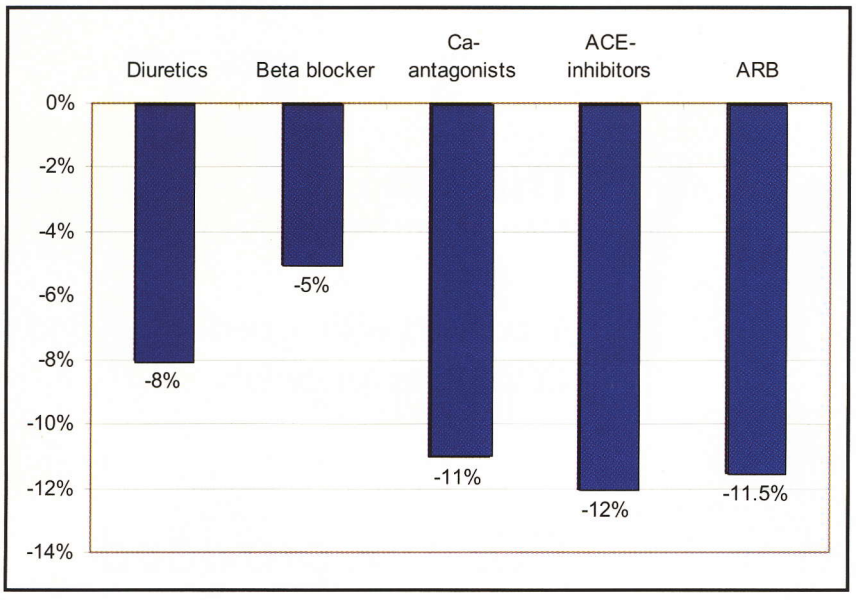
Figure 2: LV mass reduction %



Primary outcome

RR 0.87 (95% CI: 0.77-0.98)(p=0.02). Losartan significantly reduced the composite endpoint. (CV Death: MI; Stroke) Stroke: RR 0.75 (95% CI: 0.63-0.89)(p=0.001) RRR stroke: 25%. There was a significant relative risk reduction of stroke with losartan compared to atenolol.

ii. Adverse events in hypertension and hypertension management

a. Sexual dysfunction

ARB's do not worsen sexual dysfunction and may actually improve it.

b. Headache

In a systematic review and meta-analysis of 27 studies (12 110 patients), the use of an ARB for the treatment of mild to moderate hypertension reduced headache by 19% (OR 0.81 [95% CI: 0.68-0.93])

iii. Isolated Systolic Hypertension (ISH)

ARB's were shown to be beneficial and the LIFE-trial also had a sub-study on ISH, which demonstrated a significant mortality reduction with losartan.

II. RENOPROTECTIVE EFFECTS OF ARB'S

According to the U.S. Renal Data system, diabetes mellitus is the number one cause of end-stage renal disease (ESRD). Hypertension is the second most common cause of ESRD. Moreover, hypertension develops in most patients with diabetes during their cause. Lowering of blood pressure correlates with slowing of renal disease progression, making control of BP in the presence of renal disease essential.

The question, after control of BP, is whether there will be additive benefit if the renin-angiotensin system is blocked. Proteinuria in diabetic and non-diabetic patients is seen as a risk factor for progression of renal disease and lately as a risk factor for cardiovascular disease.

Angiotensin II plays an important role in the pathophysiology of renal disease and the progression to end-stage renal failure [EDRD].

ACE-inhibitors demonstrated significant reduction of the progression of diabetic nephropathy and at present, the JNC VI recommends ACE-inhibitors as first-line therapy in patients with hypertension and renal dysfunction. ACE-inhibitors also have renoprotective effects in type 1 diabetes mellitus with proteinuria and mild renal insufficiency.

Experimental data using diabetic rat models suggest that ARB's have similar beneficial effects to the ACE-inhibitors.

Clinical trials with ARB on renoprotection

A. IRMA 2: ARB effect on diabetic nephropathy in type 2 diabetes with hypertension

Irbesartan significantly reduced urinary albumin excretion rate in type 2 hypertensive diabetes mellitus patients (N=590) with micro-albuminuria in dose of 300 mg/day (not 150 mg/day) and lowered the risk of progression to persistent albuminuria by 70% over a two-year period compared to conventional treatment.

B. Irbesartan diabetic nephropathy trial (IDNT)

Hypertensive diabetic (T_2DM) patients (N=1715) with nephropathy (proteinuria) were randomised to irbesartan (300 mg/d) or amlodipine or placebo and treated for 2,6 years. The endpoint was a composite of doubling of baseline serum creatinine, onset ESRD or serum creatine of at least 530 µmol/ℓ. Treatment with irbesartan was associated with a risk of the primary endpoint that was 20% lower than the placebo group and 23% lower than the amlodipine group. There was no significant difference in the rates of death (total mortality) in any of the groups.

C. Renaal: Primary composite endpoint

In this trial, 1513 patients with nephropathy and type 2 diabetes mellitus were studied. Patients received losartan or placebo as anti-hypertensive therapy. There was a 16% lower risk for reaching the primary endpoint in the losartan group than placebo. Some of the patients treated with losartan, 43.5%, reached the primary endpoint (doubling of S-creatinine, ESRD or death) vs. 47.1% of the patients on placebo. ***See Figure 3.***

D. Marval 322 T_2DM with microalbuminuria

i. Valsartan vs. amlodipine: Valsartan was better than amlodipine in lowering urinary albumin excretion (56% of baseline vs. 92% of baseline). More patients reversed to normo-albuminuria with valsartan (29,9% vs. 14%)(p=0.001) than with amlodipine.

ii. In a study of T_2DM patients with hypertension and normotensive diabetes, all with microalbuminuria, treated with valsartan or captopril or placebo over 52 weeks, demonstrated a significant reduction of

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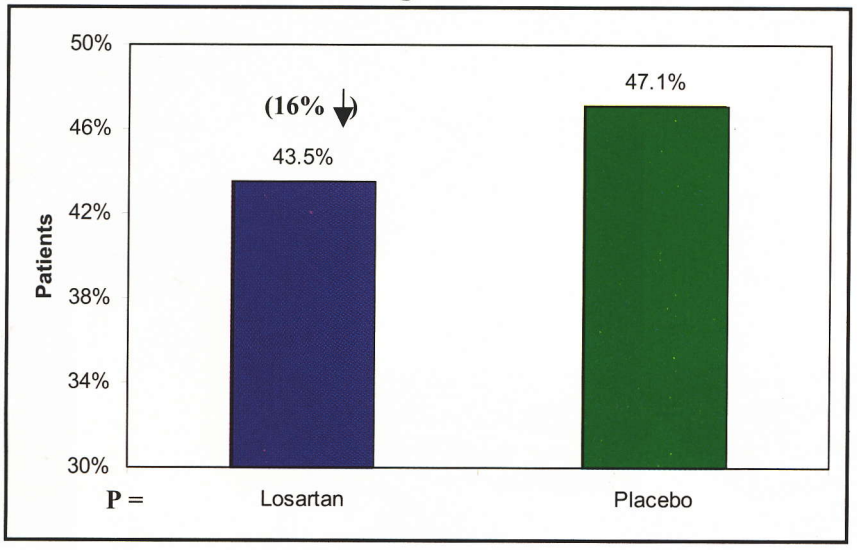
Figure 3



albuminuria in the valsartan and captopril group which are comparable vs. placebo.

E. Combination of ARB's with ACE-I renal disease

i. Cooperate Study (336 non-diabetic renal disease (proteinuria))

The results demonstrated development of endpoints in a 23% reduction of both losartan and trandolapril but when combined only 11% reached this endpoint. This is an exciting development whereby combining two different agents affecting the RAAS were more effective than either agent alone. More such studies are under way.

ii. Candesartan and lisinopril microalbuminuria study [CALM]

This was a randomised controlled trial on patients with T_2DM with hypertension and microalbuminuria over 24 weeks. The reduction in urinary albumin:creatinine ratio with the combination candesartan and lisinopril was greater than with either alone.

III. RETINOPROTECTION

A. Euclid-retinopathy

This trial demonstrated the protective effect of lisinopril (ACE-Inhibitor) on retinopathy of diabetics. The candesartan trial (DIRECT) will evaluate the effect of ARB on retinopathy. At present there are no data available.

IV. HEART FAILURE

In chronic congestive heart failure, inhibition of the renin-angiotensin-aldosterone system by ACE-inhibitors improves survival, decreases morbidity, improves exercise capacity, improves quality of life and improves left ventricular size and function.

The use of ARB's in the treatment of heart failure has been slow in evaluating hard endpoints, but a recent meta-analysis involving 12,469 patients in seventeen trials including losartan, irbesartan, eprosartan, valsartan and candesartan could not confirm that ARB's are superior in reducing all-cause mortality in patients with chronic heart failure when compared with ACE-I.

A. Elite II

Losartan was used vs. captopril, but the result of R.R. = 1.13 (95% CI: 0.95-1.35)(p=0.16) did not demonstrate the superiority of losartan over capropril for the treatment of heart failure.

B. Valsartan in heart failure [VAL-HEFT]

Overall mortality was similar in both groups RR 1.02 [95% CI:0.88-1.18] but morbidity, with an RR 13.2% (p=0.009) in the subgroup without ACE-I background, demonstrated an RRR of 44% (p=<0.0002). Mortality reduction in subgroup without ACE-I background showed an RRR of 33% (compare the 27% Enalapril Consensus 1987 study).

C. Valsartan

Valsartan effect on mortality/morbidity in heart failure patients not receiving an ACE-I were tested in a subgroup of 366 patients. Total mortality/morbidity was reduced by valsartan by 44% i.e. RR 0.56 [95% CI: 0.39-0.81](p=<0.001).

D. Charm trial program

Candesartan used in various arms for the treatment of heart failure is being tested. No results have been published yet.

E. Resolved-randomised evaluation of strategies for left ventricular dysfunction [Resolved]

This pilot study compared the effects of candesartan, enalapril and their combination on exercise performance, ventricular function, quality of life, neurohormones and tolerability.

Candesartan was as effective as enalapril. The combination of candesartan plus enalapril was more beneficial for preventing LV remodelling than either candesartan or enalapril alone.

V. BRAIN

Cerebro-protective effects of AT_1-receptor blockers

The proportion of elderly people in the general population world-wide is increasing. Cerebrovascular disease (stroke, ischaemic white matter disease) resulting in varying degrees of brain dysfunction, including dementia, represents an important chronic health problem. Important risk factors are age, atherosclerosis and hypertension. Hypertension as a cause of dementia has received some attention because of increasing evidence that hypertension may contribute to the development of dementia, although there is no agreement on the mechanism.

Previous results from anti-hypertensive trials emphasize that treatment of hypertension may be a potential way to prevent dementia. This was the basis for the SCOPE trial in which 4946 patients were studied. Candesartan vs. placebo was used with open label anti-hypertensive therapy added as needed. Cardiovascular events were non-significantly reduced by candesartan

10.9% [95% CI: -6 to 25.1%](p=0.19). All strokes were reduced by 23.6% [95% CI: -0.7 to 42.1](p=0.056) and non-fatal strokes reduced by 27.8% [95% CI: 1.3 to 47.2] (p=0.04). The stroke reduction was significant. The reduction in dementia was not different in the two treatment groups.

Prophylactic treatment of migraine with AT_1 receptor blocker

Randomised controlled trial with candesartan vs. placebo in migraine patients.

Primary endpoint: Number of days with headache. Candesartan significantly reduced the number of days with migraine (p=0.001).

SUMMARY

For many clinical situations where the RAAS needs to be affected by treatment, the ACE-Inhibitors are used. Increasingly, new data are being published to demonstrate morbidity and mortality reduction by the angiotensin receptor blockers. We still need more data to be sure of the exact role of the ARB's, however, emerging clinical indications indicate a role to be played by the ARB's.❐

Please refer to the CPD Questionnaire on page 71

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